The Journal of Allergy

VOL. 13 JULY, 1942 NO. 5

Original Articles

SKIN REACTIONS

XV. QUANTITATIVE STUDIES OF WHEALING

H. A. ABRAMSON, M.D., M. G. ENGEL, M.A., AND H. H. GETTNER, M.S.
NEW YORK, N. Y.

IT APPEARS desirable at this time to report the progress made in the more precise development of a contour gauge previously described.[1] The new technique facilitates the elucidation of the mechanisms underlying the disappearance of papules in the skin whether liquid is directly injected or whether a wheal is produced by physical or immunologic means.

In some unpublished experiments[2] dealing with the mechanism of the apparent disappearance of wheals produced by physiologic salt solution (McClure-Aldrich), it was found that if such a solution was injected intradermally into an area rendered edematous by previously injected physiologic salt solution, the wheal so produced spread mechanically rather quickly because of the changed physical structure of the tissue. In other words, the redistribution of the liquid following injection was apparently as important a factor as absorption of the liquid in the "disappearance" of the wheal. The development of the method to be described here has resulted in a semiquantitative technique for following the nature of the redistribution of liquid following intradermal injection into the skin.

The contour gauge already described[1] consists of movable square pencil leads* held vertically by a plunger between glass slides. Direct contact prints were made from the displaced leads and the height of the wheal was taken as a quantitative measure of the intensity of whealing or the rapidity of liquid disappearance. In this paper, further modifica-

From the Medical Services of Dr. George Baehr and the Laboratories of the Mount Sinai Hospital, and the Department of Physiology, College of Physicians and Surgeons, Columbia University.

This investigation has been aided by a grant from the Josiah Macy, Jr., Foundation.

*Eversharp.

tions are described, and some data are presented. These new modifications make the method more precise and considerably widen the scope of its application. Of especial interest is the fact that the point of view regarding the importance of redistribution of liquid in the dermis is confirmed.

METHODS

The general construction and use of the contour gauge is described in a previous communication. Certain modifications in the technique as a whole are described here. A more regular contour can be obtained by grinding flat the ends of the leads against the base of a fine grinding wheel. The glass slides are 1 by 4 inches. The number of leads vary from twenty-five to sixty. In some instances it is desirable to construct longer instruments when the spread of the wheal is very great.

Instead of seeking a flat surface of the forearm and assuming that the base of the contour was straight, a new technique was adopted. The contour of the forearm, itself, was obtained by holding the crook of the elbow at a given angle and always having the fingers in the same position by grasping an article about the size of a baseball. In this way, the tensions on the skin of the forearm remained the same during the measurements. The subject is kept seated during the experiment, and no undue movement of the forearm is permitted unless the effect of movement, itself, is studied. When the gauge is first placed upon the forearm, two short lines are drawn upon the skin at both ends of the instrument. A line is also placed at right angles to one end of the instrument to be sure that the ends always connect the same two points.

After the base line is obtained, the contour gauge used to obtain the base line is put into an enlarger and the base line, itself, projected upon photographic paper. In this way the shape of the base line is obtained and recorded. The base line, itself, is then cut out and the contour of the arm thus obtained is used in subsequent studies on that particular line of the forearm. It is, of course, necessary to return each time to the same reference points described above.

An Eastman Kodak home enlarger with a red filter was modified to enlarge the image of the contour gauge. The ordinary lamp was taken out and a No. 1 Photoflood was installed. This heats the apparatus considerably, and it is necessary to provide extra ventilation. We have found that a magnification of ×3 provided useful images for our experiments. "Rapid Velox F 4, glossy" and an exposure of about ninety seconds was used with single strength MQ developer. The development took about forty seconds and was observed by red light until the desired contrast was obtained. The frame of the enlarger is readily adapted to take the gauge. By projecting the contour of an experimental wheal against the base line, obtained as described in the foregoing, the eleva-

tion of the skin is obtained directly. In this way the image is a direct measure of wheal growth or wheal disappearance. The only error which can occur without detection in getting the wheal elevation to fit the base line is a smaller value of the wheal area.

In previous studies we have been satisfied with studying the height of the wheal. A better measure of wheal formation is evidently given by the area of the contour image. It would be more desirable to obtain a volume for more precise work. An approximate volume of wheal elevation above the skin could probably be calculated. In the present studies this development has not been made. To obtain a measure of wheal volume above the skin, a rapid method was devised for weighing the cutout contour images. Rather than using a quantitative balance, a thin strip of spring steel, 0.0015 inches thick, was extended from a fixed point and calibrated with ordinary weights.

The balance reading was 0 to 50 mg. with a deflection varying approximately from 2 mm. per milligram at the beginning of the deflection to about one-half as much at the end. A balance of this type may be used over a period of three months without much change in the zero point. The scale was made movable so that adjustment of the zero point may be obtained.

For the method just described, not alone is the white area of the skin, ordinarily called the wheal, outlined, but also the adjacent edematous area which spreads out from the sharp edge of the blanched area itself to merge gradually with the base line. This will be evident when our data are examined. It is evidently of great importance that the base line be fitted accurately to the actual base of the blanched area, ordinarily called the wheal, because the blanched portion only indicates the amount of tension which has been developed and not the amount of fluid which is necessary to produce that tension in the wheal itself and in the surrounding tissues.

Fig. 1.—Actual size of elevation obtained by magnification of contour gauge displacement. This is three times the natural size of the elevation twenty minutes after electrophoresis of 1:50,000 histamine. Current density, 0.5 ma.; electrode area, 1 sq. cm.

EXPERIMENTAL

Histamine.—Fig. 1 is the actual size of an elevation recorded by the photographic technique described under Methods. This is three times the natural size observed twenty minutes after the electrophoresis of 1:50,000 histamine on the anterior aspect of the forearm of the subject studied in Fig. 2*A*. *A*, *B*, and *C* of Fig. 2 are some of the record obtained with the contour gauge in a series of experiments on wheal formation on the anterior aspect of the forearm following electrophoresis

of different concentrations of histamine. At the top of Fig. 2 the concentration of histamine is indicated. The time of measurement is alongside the elevations for all of the wheals at corresponding times. Wheaing was therefore observed from three to 120 minutes. As indicated in

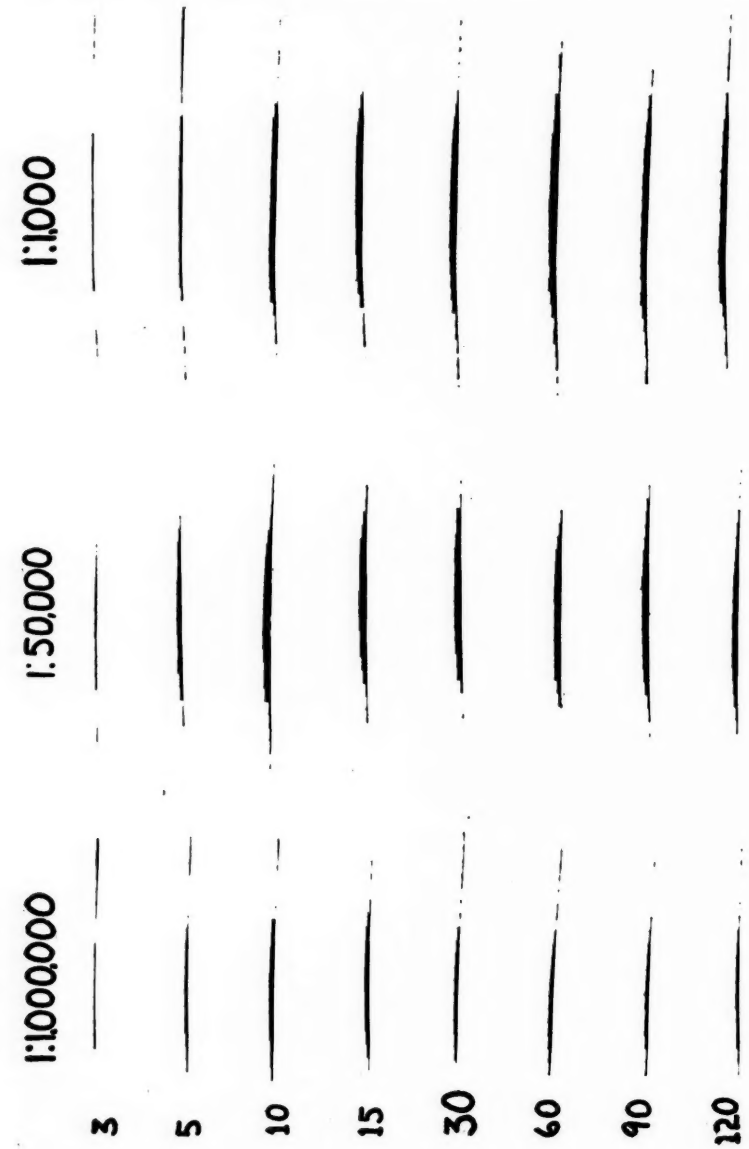


Fig. 2.—*A*, *B*, and *C* are reductions of elevations obtained with the contour gauge following the electrophoresis of 1:1,000,000, 1:50,000, and 1:1,000 histamine from 3 to 120 minutes after application of the electrode. Time of application of current, 3 minutes; current density, 0.5 ma.; electrode area, 1 by 1 cm. The site of application was the anterior aspect of the forearm of the same individual in the three series of experiments.

the part on Method, the original magnification was ×3. The photograph is reduced to natural size in this figure.

Electrophoretic introduction of the histamine was employed for the following reason: In general, it may be rather difficult to make quantitative studies of wheaing with intradermal injections of histamine diluted

to 1:1,000,000.[3] This is because of the possibility that the needle may be inserted into the skin at different levels. The electrophoretic method, however, eleminates this source of error; that is, the material is always introduced at the same level with the electric field.[4] Fig. 2*A* is the reaction of the skin to electrophoresis of 1:1,000,000 histamine. The electrode in Fig. 2*A* as well as in *B* and *C* was 1 by 1 cm. in area. Using a current of 0.5 ma., the time of application was three minutes. Note in Fig. 2*A* that there is a slight but definite elevation of the skin which reaches its maximum about fifteen minutes after the histamine is introduced. The whealing response was evident even after two hours in spite of the fact that a very small amount of histamine is introduced in this way. Fig. 2*B* on the same subject with 1:50,000 histamine showed an increased size of the wheal and a greater degree of spreading. The actual size of the electrode in Fig. 2*A* is indicated roughly by the size of the wheal. The spreading in Fig. 2*B* is due to two factors: (a) the transport of the histamine through the lymphatics to adjacent areas followed by the escape phenomenon of McMaster[5] leading to additional whealing as well as (b) mechanical spread due to an increase in intradermal pressure. The maximum reaction was again apparently reached ten to twenty minutes after the administration of the drug. The fact that the wheal does not disappear even after two hours is more evident than in Fig. 2*A*. When the wheal is observed directly without the use of a contour gauge, a more sharply demarcated elevated border is observable. However, the contour gauge does not indicate that such sharp borders exist in the dermis in this type of whealing. The border of the wheal merges more directly with the surrounding tissues. Fig. 2*C* is an example of the more massive spread of the wheal following electrophoresis of 1:1,000 histamine. At the end of fifteen minutes the wheal has not spread very much. However, a good deal of spreading and redistribution of wheal liquid occurs so that at the end of several hours, the area of the elevation is still readily observed.

These experiments illustrate the delicacy with which the contour gauge observes slight changes in the level of the skin surface.

The magnified duplicates of the contours illustrated in Fig. 2*A*, *B*, and *C* have been cut out and weighed. These weights have been plotted in Fig. 3 as a function of time for the different concentrations of histamine. This quantification results in a much clearer picture of the way in which whealing proceeds here. A maximum elevation area was reached within twenty minutes, independent of the concentration. At the end of two hours following a gradual fall, the elevation area is still quite high. It is of great interest that the slope of the decrease of the elevation area with all three concentrations of histamine does not appear to be very different using this method of plotting. If the reaction to histamine is greater, however (Fig. 8) the disappearance rate is accelerated slightly. It may be argued that the elevation area is not a true measure of the volume

of the wheal and that a better measure would be the elevation area multiplied by some function of the length of the contour elevation given in Fig. 2*A*, *B*, and *C*. This argument is certainly correct, and no further quantitative significance should be given to our plot except that it is a better measure of whealing than has been obtainable up to the present. The qualitative significance of the data plotted in Fig. 3 can be summarized as follows: Although the wheal begins to disappear shortly after it reaches its maximum, this disappearance is fairly slow in the normal individual, with a good sized elevation remaining at the site of application of the histamine two hours after the administration of the histamine, even when the histamine administered has been as low as 1:1,000,000, with our technique.

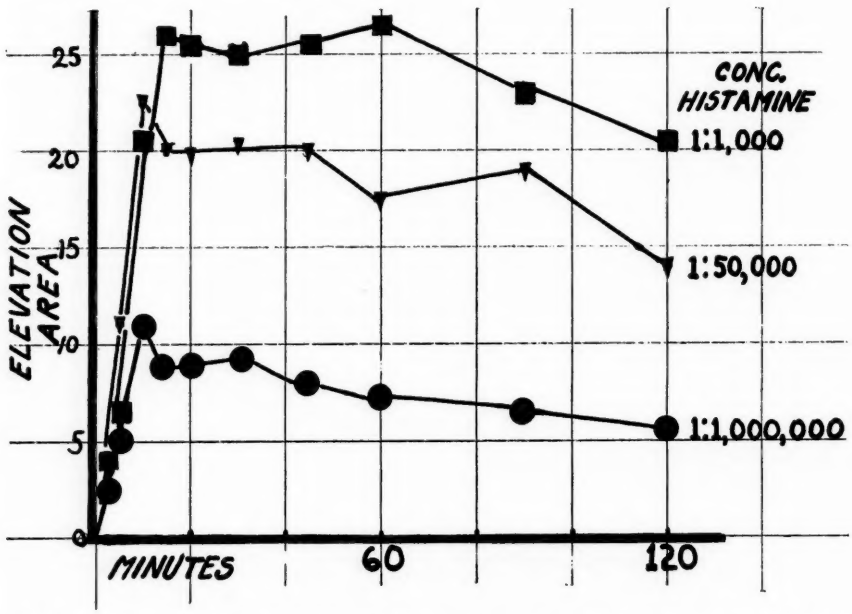


Fig. 3.—The magnified duplicates of the contours illustrated in Fig. 2 *A*, *B*, and *C* have been cut out and weighed. These weights have been plotted in Fig. 3 as a function of time for different concentrations of histamine.

Whealing in Light Hypersensitiveness.—Not all wheals spread in the way indicated in Fig. 2*B* and *C*. In Fig. 4 are unreduced elevations obtained from two and one-half to sixty minutes following the irradiation of the anterior aspect of the forearm of a patient with urticaria solaris. Note the size of the wheal at the end of twenty minutes. The length of this wheal is a little more than 4 cm. at the end of that time. Although at the end of one hour the wheal height has increased and the weight of the elevation has become greater, the spread is very slight indeed. In other words, the lateral redistribution of the liquid in a wheal need not necessarily accompany whealing to a very great extent. At certain phases of the whealing process, elevation of the skin may be the dominant

feature. The redistribution of liquid in the histamine wheal is probably essentially dependent upon the absorption and escape[6] of the histamine through contiguous capillary lymphatics. The adjacent dermis is thereby filled with liquid which offers less resistance to the spread of the liquid from the original site. The nature of the wheal produced by light indicates that a nondiffusable substance rather than histamine is responsible for the whealing reaction.

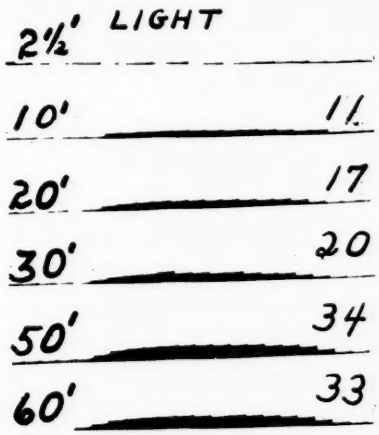


Fig. 4.—The anterior aspect of the forearm of a case of urticaria solaris was irradiated with ultraviolet light. Note the slower growth of the wheal with very little spreading, although the height of the wheal increased markedly. The time in minutes is given on the left side of the diagram, whereas the weights of the unreduced contours are given on the right side.

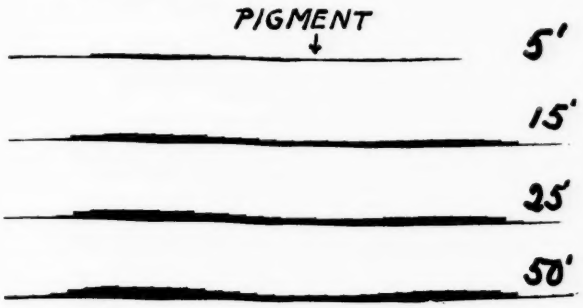


Fig. 5.—The same patient illustrated in Fig. 4, pigments after application of ultraviolet. The anterior aspect of the forearm was irradiated on both sides of a pigmented zone. Note the zone of pigmentation. Definite retardation of whealing has occurred. The pigment, however, did not protect completely against the urticarial response to ultraviolet. The time in minutes is given on the right side of the diagram. Note in this instance also that in spite of the deposition of liquid in the tissues, the lateral spread of the wheal and therefore the redistribution of liquid is negligible. In this type of whealing response as well as that in Fig. 4, no pseudopods ever formed.

In Fig. 5 is the effect of pigmentation on elevation of the skin in urticaria solaris. The concavity in the central portion of each of the wheals is a zone of pigmentation. The records were taken at five, fifteen, twenty-five, and fifty minutes. These data also indicate dramatically the sensitivity of the method and the absence of any marked redistribution of liquid in the large wheals observed in urticaria solaris.

Injected Liquid.—Fig. 6*A* is an experiment on the change in contour of wheals produced by the injection of physiologic saline and Fig. 6*B* that of distilled water. Fifteen hundredths of a cubic centimeter was injected intradermally in each case. There is a marked difference in the

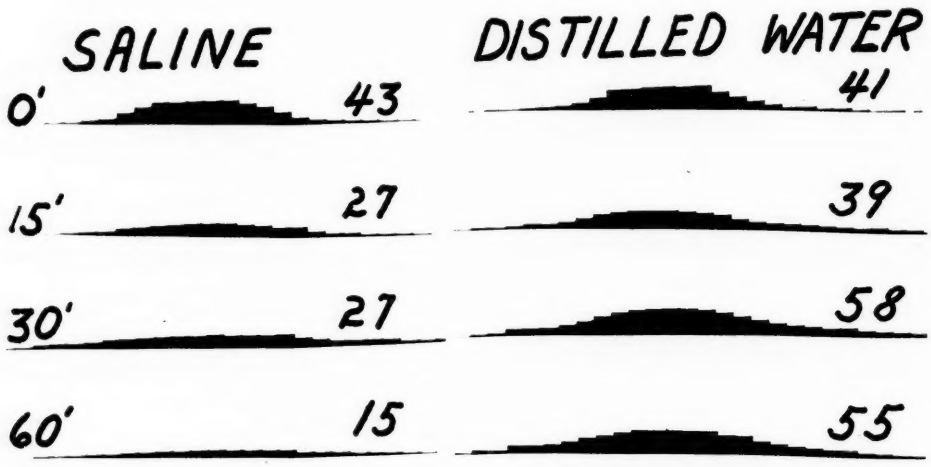


Fig. 6.—Fifteen hundredths of a cubic centimeter of physiologic saline was injected intradermally into the anterior aspect of the forearm. The time in minutes is given on the left-hand side of the figure for both *A* and *B*. On the right-hand side the weights of the elevations are recorded. Note in *A* the rapid drop in the height of the wheal with a redistribution of liquid in the adjacent tissues followed by disappearance of about two-thirds of the liquid above the surface of the skin.

B, The results obtained with the use of distilled water are very different from those obtained with saline. There is a marked increase in the volume of injected liquid as well as a lateral spread of the initial papule.

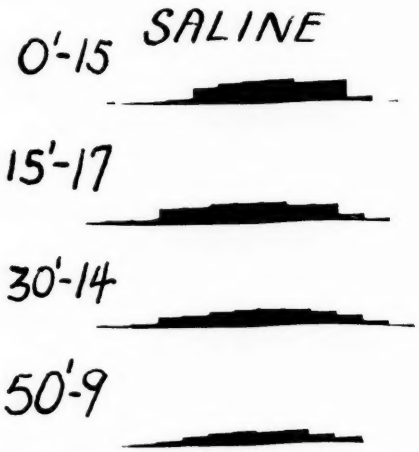


Fig. 7.—Record of saline disappearance from injection of only 0.05 c.c. The numerals following the time in minutes are relative values of the elevation areas.

reaction of the skin to these two solutions. In the case of the saline, in this instance, there is a drop in the height of the wheal followed by a redistribution of the liquid. The relative areas of the elevation are given

below each elevation. Note that in the case of the saline, the weight of the elevation contours decreased from forty-three to fifteen at the end of an hour. Following the injection of distilled water, there was a slight change in the height of the wheal followed by a transudation and spread of fluid so that at the end of one hour there was about a 30 per cent increase in the elevation area. Since these processes also occur beneath the base line of the skin, we can be certain that at least the type and amount of change (redistribution) observed has occurred. This experiment was done in a case of rheumatic heart disease with mitral insufficiency.

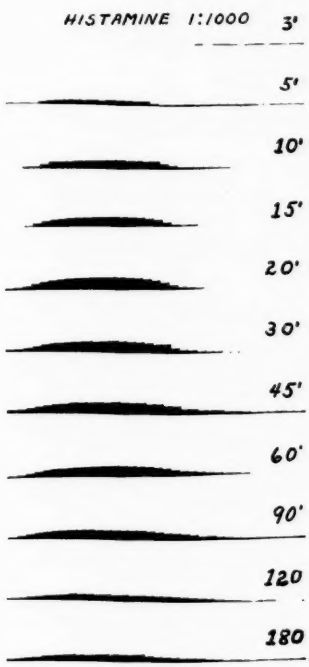


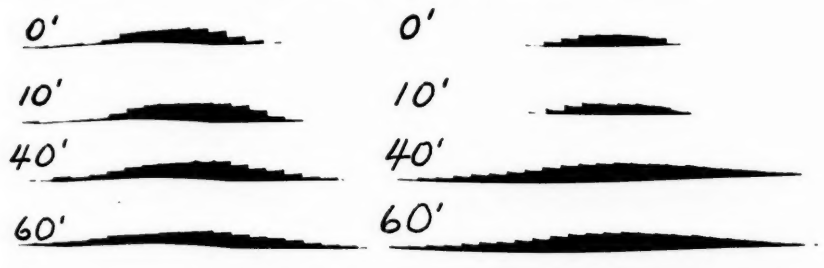
Fig. 8.—Showing another type of response of the skin of the anterior aspect of the forearm with the same technique of applying histamine illustrated in Fig. 2C. In this case the whealing response is much greater, and the lateral spread of the wheal and redistribution of the liquid are much more marked. The rate of the decrease of whealing is also faster than that illustrated in Fig. 3 for different concentrations of histamine. The weights of the contour elevations for the various times are as follows:

TIME (MIN.)	WEIGHT (MG.)
5	17
10	39
15	46
20	75
30	73
45	70
60	64
90	54
120	41
180	39

Fig. 7 is an experiment in which only 0.05 c.c. of physiologic saline was injected (into a patient with atherosclerosis and angina pectoris). At the end of fifty minutes there is observed the redistribution

phenomenon with the relative area of the elevation area dropping from fifteen to nine units.

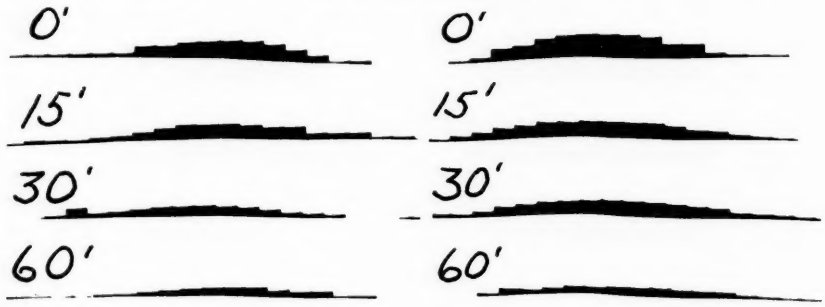
Miscellaneous Experiments.—The data of the preceding section illustrate that the contour gauge combined with the new photographic technique of enlargement offers the investigator a quantitative method of studying qualitative and quantitative differences in the nature of the whealing processes. In this final experimental section, we would like to illustrate some other types of experimental work in progress.



A. *B.*

Fig. 9.—*A*, The record following the injection of 0.1 c.c. of 1:1,000,000 epinephrine in saline.

B, 0.1 c.c. of 1:1,000,000 histamine in saline has been injected on the same patient illustrated in *A*. When extreme reactions of the type illustrated in *A* and *B* occur, it is important to rule out the presence of dermographism. It is not known whether this patient showed dermographism or not and this figure is given not to indicate that they are typical reactions to these drugs but to illustrate types of experiments which may be worked out by means of the technique described.



A. *B.*

Fig. 10.—*A* should be compared with *B*. Fairly rapid disappearance of 0.1 c.c. physiologic saline.

B, In this experiment the same volume (*A*) of 2 per cent saline was injected. Note the difference in the size of the initial papule. Whether this was due to the needle being at a different level or whether due to the rapid inflow of tissue fluid into the 2 per cent saline is not known.

Claims have been made that different individuals vary in their sensitivity to histamine. We would rather say that they vary in their whealing response to histamine. Whether in any instance this is (1) pharmacologic response of the blood vessels, (2) an anatomic accident leading to variation in histamine distribution in the skin, or (3) superimposed dermographism must be distinguished. In any event we have also observed differences.

Fig. 8 is an illustration of a reaction of 1:1,000 histamine obtained with the same technique illustrated in Fig. 2. The experimental times

are given to the right of the pattern. Note the more intense reaction as compared with the 1:1,000 pattern in Fig. 2 as well as the fact that a good sized wheal, in fact, greater than that observed in Fig. 2, remains three hours after the experiment is begun.

A patient with ulcerative colitis (Fig. 9*A*) was injected with 0.1 c.c. of 1:1,000,000 epinephrine in saline with marked spreading of the wheal and redistribution of the liquid. Fig. 9*B* represents data on the same patient with 1:1,000,000 histamine.

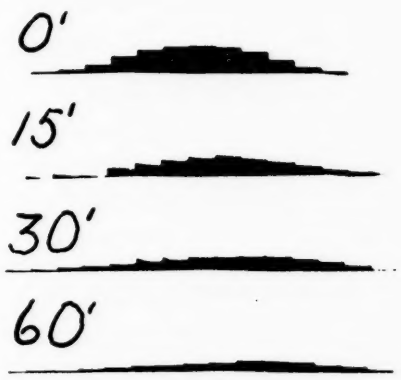


Fig. 11.—This illustrates the rather rapid disappearance of saline following the intradermal injection of 1:10,000,000 histamine in physiologic saline. It is possible as indicated in the text that the marked vasodilatation produced by this small concentration of histamine may have resulted in rapid absorption.

Fig. 10*A* and *B* are comparisons of the effect of intradermal injection of 0.10 c.c. of physiologic saline and 2 per cent saline. The anticipated osmotic effect (other effects may be present) in the stronger solution is illustrated in Fig. 10. Further confirmatory experiments are required.

Fig. 11 is of some interest because it represents the intradermal injection of 1:10,000,000 histamine. It is our impression that the injected liquid disappears more rapidly than anticipated.[3] Since histamine in this concentration produces a greater measure of vasodilatation than transudation, it is conceivable that stimulation to absorption by the blood vessels and lymphatics outweighs the rate of extravasation. This would account for the rapid disappearance of the wheal.

DISCUSSION

The data show unequivocally that changes due to redistribution of liquid in the tissues and the spreading of whealing due to absorption by and escape from lymphatics may be graphically followed by the technique employed. The experiments have been done on either normal or convalescent patients in the wards of a hospital.

It would be of great interest to standardize the patterns obtained in normal and in dermographic individuals. On the basis of these normal patterns it should be possible to explore the mechanism involved in the

absorption of liquids from edematous tissues and from tissues in individuals in shock, in dehydration, and in other states.

We believe that the type of pattern obtained in these conditions will depend upon three factors, the nature of which should be minutely explored: (1) the effect of the state of the blood vessels on absorption (this, for example, can be followed by contracting the blood vessels by epinephrine); (2) the influence of the lymphatics; (3) the gel state or structural rigidity of the tissues involved; and (4) the quantity of interstitial fluid.

The redistribution of liquid in the wheal apparently depends upon two factors: (1) the pressure exerted upon the gel structure of the dermis; and (2) the transudation of liquid or irritative processes which lead to destruction of the gel structure of the dermis. Although, for example, a good sized wheal forms in the experiments indicated in Fig. 4, the growth of the wheal is characterized by an increase in the height of the wheal rather than a lateral spread. A similar phenomenon is to be observed in Fig. 5. Stated in another way, although the intradermal pressure increases markedly, there is little or no redistribution of liquid because the contiguous gel structure of the dermis has remained intact. Compare the mechanism of the whealing process in Figs. 4 and 5 with the marked change and spread of whealing liquid when histamine is introduced in the dermis. In this case, the histamine diffuses away from the zone of introduction and is taken up by the lymphatics. The histamine then escapes from the lymphatics in areas contiguous with the wheal where the transudation of liquid leads to the spread of the wheal and to impairment of the gel structure. In this way there are formed other avenues for the more centrally located liquid to be redistributed in the zones of the dermis adjacent to the original site. A diffusible substance like histamine is evidently not present in the wheals produced by light because there is no evidence of spreading or an important redistribution of liquid. On the other hand, if the whealing process in an irradiated zone becomes sufficient to make the intradermal pressure very great, the pressure itself may lead to a lateral redistribution of the whealing liquid. A similar phenomenon occurs when the injected liquid is put in with so much pressure that the intradermal injection pressure itself destroys the continuity of the gel structure of the dermis.

SUMMARY

1. A quantitative method of following semiquantitatively the volume of whealing liquid whether produced pharmacologically or by external means is described.

2. The method makes use of the projection of the image of the displacement of square pencil leads on photographic paper against the actual base line of the wheal. By enlarging this image under standard

conditions and cutting out and weighing the elevations, a measure of the whealing volume as represented by the elevated (contour) areas is obtained.

3. This technique has been applied to the quantitative study of whealing produced by histamine and the reaction of the skin to the injection of distilled water, epinephrine, histamine, and similar pharmacologically important materials.

4. It has been shown that two factors must be followed in the study of the disappearance of whealing liquid; namely, the redistribution of the liquid following its injection and absorption of the liquid.

5. The first factor will essentially depend upon the mechanical structure of the dermis. This is probably the basis for the rapid disappearance in edema.

REFERENCES

1. Abramson, H. A., and Gorin, M. H.: Skin Reactions. V. A Contour Gauge for Measurement of Height and Breadth of Allergic Wheals, J. ALLERGY **10**: 159, 1939.
2. Fremont-Smith, F.: Unpublished data and personal communications.
3. Abramson, H. A., and Alley, A.: Skin Reactions. I. Mechanism of Histamine Iontophoresis From Aqueous Media, Arch. Phys. Ther., X-ray, Radium **18**: 327, 1937.
4. Abramson, H. A., and Gorin, M. H.: Skin Reactions. IX. The Electrophoretic Demonstration of the Patent Pores of the Living Human Skin. Its Relation to the Charge of the Skin, J. Phys. Chem. **44**: 1094, 1940.
5. Hudack, S. S., and McMaster, P. D.: The Permeability of the Wall of the Lymphatic Capillary, J. Exper. Med. **56**: 223, 1932.
   McMaster, P. D., and Hudack, S. S.: Induced Alterations in the Permeability of the Lymphatic Capillary, J. Exper. Med. **56**: 239, 1932.
6. Abramson, H. A., and Engel, M.: Skin Reactions. II. The Effect of Allergic and Histamine Wheals on the Rate of Absorption of Dyes and Blood From the Human Cutis, J. Invest. Dermat. **1**: 65, 1938.

We are indebted to the expert assistance of Mr. Alan Block who is responsible for the precision of many of these records. Dr. G. Ehrlich also aided in the experimental procedures.

INHALANT SENSITIZATION AND SHOCK IN GUINEA PIGS UNDER CONTROLLED ATMOSPHERIC CONDITIONS

II. Histamine, Histaminase, and Acetylcholine as Possible Preventives

L. J. Courtright, M.D., S. H. Hurwitz, M.D., and
Abbie Betts Courtright, B.A.
San Francisco, Calif.

IN A previous paper[1] a method was presented for the study of inhalant sensitization in guinea pigs under controlled atmospheric conditions. This method, we believe, closely parallels natural sensitization in man and gives valuable clinical information concerning the reaction of animals under direct observation in the air-conditioned chamber. We also believe this method to be of value in the study of various pharmacologic agents on the possible modification or prevention of clinical anaphylactic responses in the guinea pig under controlled conditions. This report presents our results on the influence of histamine, histaminase, and acetylcholine on inhalant sensitization and shock in guinea pigs.

Pretreatment with histamine by injection as a means of preventing anaphylactic shock in animals already sensitized has been suggested by Führer,[2] Farmer,[3] Karady and Browne,[4] Barlow and Homburger,[5] and Neely.[6] Alexander and Bottom,[7] Karady and Browne,[4] and Youngner, Freedman, and Nungester[8] supplemented these studies with observations on the effect of histaminase injected prior to the administration of the shock dose of allergen, with a view to determining whether or not histaminase could modify or prevent anaphylactic shock. All of these observations have been carried out by the use of the usual parenteral methods of sensitization and shock, with the exception of the work of Neely, who sensitized his animals by the intraperitoneal route and shocked them with a solution of egg white sprayed into a chamber, a technique which approximates in some respects the inhalation method employed by us.

The use of another potent pharmacologic agent as a means of modifying local tissue reactivity was suggested by the work of Pearson.[9] This observer used daily injections of mecholyl over a period of twenty to sixty days in wheat-sensitive patients prior to a test ingestion of wheat. In most of these patients, who were followed for over a year, there appeared to be a protective action. In our experiments we studied the effect of acetylcholine alone and acetylcholine with histamine injected throughout the experimental period.

From the Department of Medicine, Stanford University School of Medicine.
This study was supported in part by funds from the Rockefeller Foundation.

METHOD

Healthy female guinea pigs, 200 to 300 Gm. in weight, were used in all experiments. The dose and time of injection of histamine, histaminase, and acetylcholine bromide are given in detail in the charts. Both the pretreated and control pigs were sensitized by exposure to dry horse dander powder (0.1 to 10 μ), as described in a previous paper,[1] under air conditions of 90 to 94° F. and a relative humidity of 35 to 40 per cent. One-tenth of a gram of dry dander was puffed in every five minutes, while the circulation of air was maintained at 0.15 cubic feet per minute. Most of the animals were exposed in the chamber one hour a day for approximately seven days. One to two weeks later they were re-exposed to the dander under the same atmospheric conditions. At all times the outside weather was checked for any gross change which might affect the reactions. It was found that 85 to 90 per cent of the untreated guinea pigs so sensitized showed definite if not violent respiratory anaphylaxis. At the end of each experimental period, the surviving pigs, with the exception of the histaminase group, were injected intrajugularly with 0.5 c.c. of horse dander extract as a final test of their sensitivity.

EXPERIMENTAL DATA

Experiment 1.—Five guinea pigs, as shown in Fig. 1, were injected intraperitoneally with from 0.1 to 0.2 c.c. of histamine diphosphate* almost every day for approximately one and one-half months. Sensitizing exposures in the chamber to dry horse dander were begun eight days after the first histamine injection. Exposure took place one hour a day for seven hours through an eight-day period for both the five pretreated and five control animals. After a two-week incubation period both the control and pretreated animals were again exposed to the dry dander in the chamber. Two of the pretreated animals had severe expiratory dyspnea. Two of the control animals also had severe dyspnea, and two had questionable symptoms. Re-exposure at various intervals produced typical anaphylactic reactions in both groups. On one occasion the usual dose of histamine caused anaphylactoid reactions and two deaths. On the final intravenous injection of horse dander extract, two of the remaining three histamine-treated animals died in anaphylactic shock, while four of the five control animals likewise died in shock.

Experiment 2.—The six treated animals shown in Fig. 2 were injected intraperitoneally with 0.1 to 0.15 c.c. of histamine diphosphate, 1:1000 solution, for fourteen days through a fifteen-day period. On the tenth day after the first injection the six experimental and six control animals were given sensitizing exposures to horse dander one hour a day for seven days through an eight-day period. Three days after their last sensitizing exposure, re-exposure produced severe anaphylactic reactions

*Ergamine, Burroughs, and Wellcome Co. 1:1000 solution representing 1 mg. of histamine diphosphate per cubic centimeter. In our experiments all doses of histamine and acetylcholine bromide were measured as the salt.

in four each of the pretreated and control pigs. Both groups were re-exposed approximately once a week for two and one-half months. Severe reactions took place in both sets of animals. Two of the control pigs

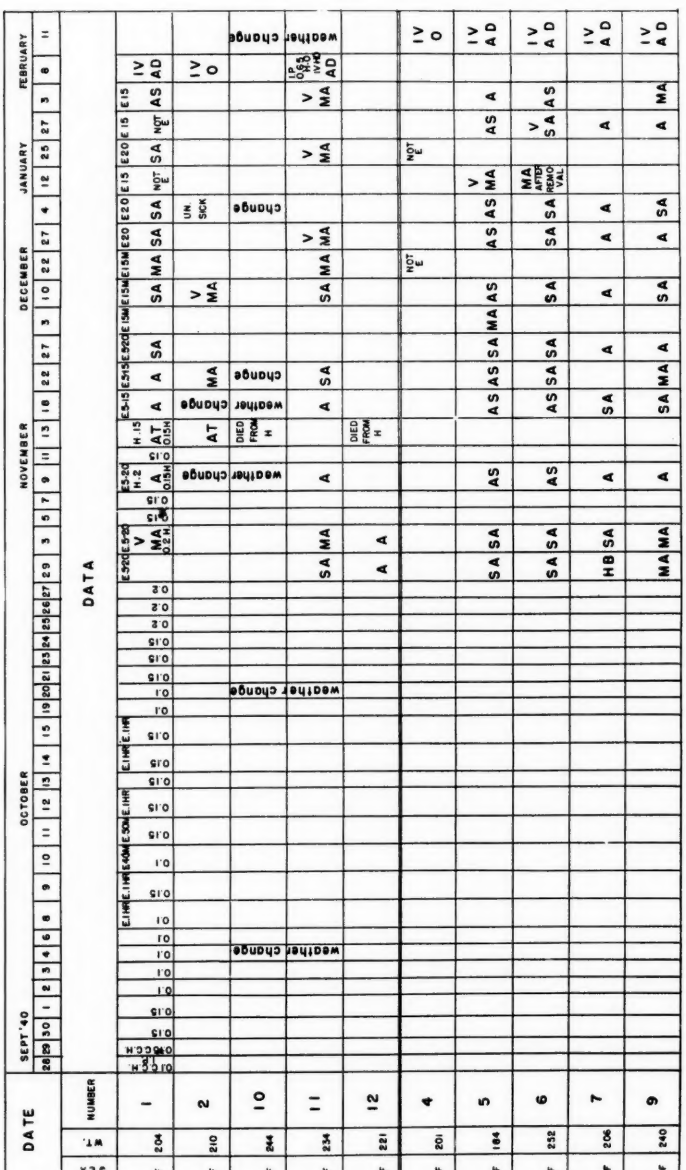


Fig. 1.—Day-to-day data on injections of histamine diphosphate; inhalation sensitizing exposures to horse dander powder and reactions of both injected and control animals. *A*, Expiratory dyspnea (experimental respiratory anaphylaxis); *AD*, anaphylactic death; *AS*, anaphylactic shock; *HB*, heavy breathing, not definite anaphylaxis; *MA*, mild expiratory dyspnea; *SA*, severe expiratory dyspnea; *VMA*, very mild expiratory dyspnea; *IV*, intravenous injection; *AT*, anaphylactoid reaction; *E*, exposed; *H*, histamine.

died in shock from inhalation exposure. Final intravenous injection three and one-half months after the beginning of the experiment revealed no differences in reaction between the control and histamine pretreated animals.

Experiment 3.—In the six experimental animals reviewed in Fig. 3, histamine hydrochloride was used. A solution was prepared which represented 2 mg. per cubic centimeter. Doses increasing from 0.03 to 0.5 c.c. were given intraperitoneally each day through the first eight

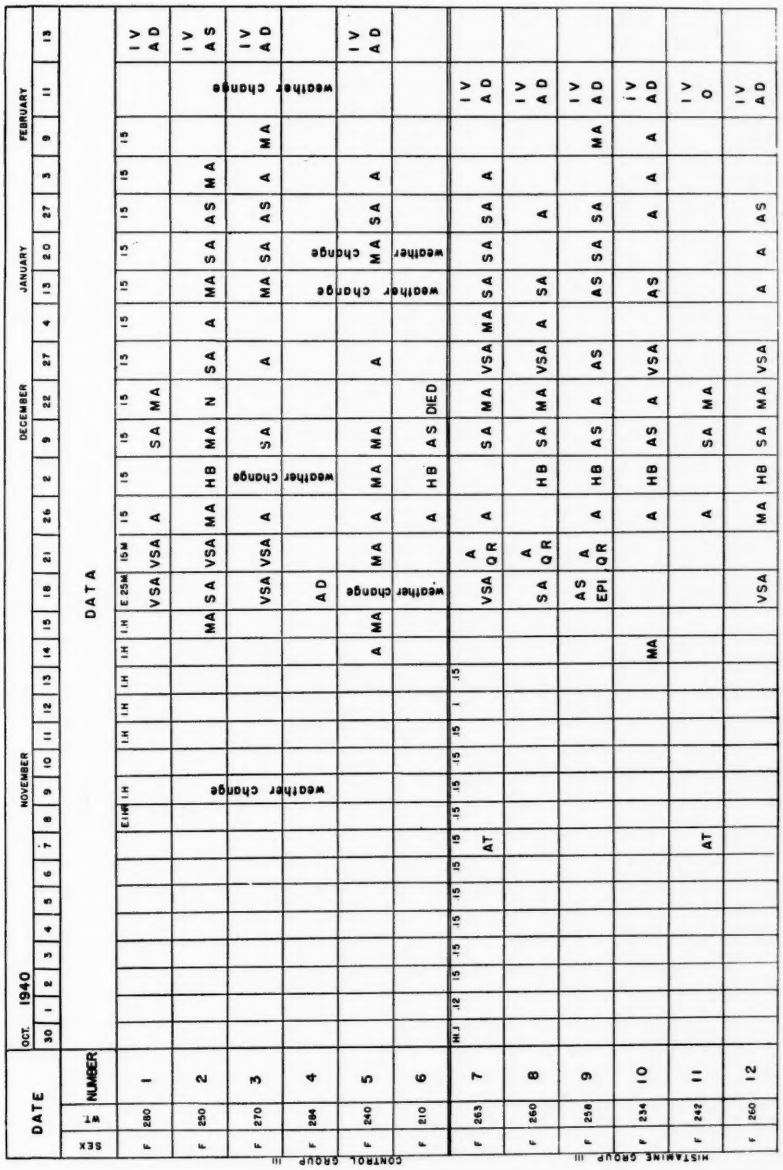


Fig. 2.—Legend as in Fig. 1; *EPI*, epinephrin; *QR*, quick recovery; *HI*, histamine; *H*, hour.

days of the experiment. After this, 0.5 c.c. was used. Beginning on the fifth day of the experiment, sensitizing exposures to dry horse dander were begun. Injections were made fifteen minutes before the sensitizing exposures. A total of five hours was given to both the four control and

six pretreated animals during a thirteen-day period. All exposures except one lasted but thirty minutes. After a two-day rest, re-exposure three times on three successive days caused mild but definite symptoms of anaphylaxis in the control group but none in the pretreated animals. Histamine injections were then discontinued. After a lapse of nineteen days the pretreated guinea pigs without the preliminary histamine injection and the control animals were again exposed in the chamber. On this occasion two of six histamine-treated animals showed moderate anaphylactic symptoms, while two of four control animals died in anaphylactic shock, a third showing violent clinical symptoms. Two weeks later histamine injected before the exposure did not seem to modify the anaphylactic reactions, as four of the animals had definite symptoms.

Two years later we duplicated this experiment in every detail. Six control and six histamine-treated guinea pigs were sensitized. After the thirteen-day period of sensitization and a two-day rest, re-exposure for three successive days revealed the following reactions: On the first and second days the histamine-treated animals showed no definite reactions, although one did die from the histamine injection. However, definite mild expiratory dyspnea occurred in all members of the control group. On the third day, comparable to July 31 in Fig. 3, four control animals had definite symptoms, while one of the histamine-treated animals showed severe expiratory dyspnea and another one mild expiratory dyspnea. Nineteen days later, exposure on a day comparable to August 19 in the experiment as shown in Fig. 3, one control animal had anaphylactic death; two others had anaphylactic shock, near death; one had anaphylactic shock; and two had very severe respiratory anaphylaxis. Of the pretreated animals without their preliminary histamine injection one had anaphylactic shock, and the four others had moderate respiratory anaphylaxis. These observations would suggest that some protection against clinical symptoms of anaphylactic shock may result from the injection of large doses of histamine just prior to a subsequent exposure to horse dander in the chamber.

Experiment 4.—The experiment detailed in Fig. 4 affords a comparison between the effect of pretreatment with histamine given over a long period of time in increasing dosage and that of moderately large doses injected just prior to exposure. For one month before sensitizing exposure six animals were given histamine hydrochloride every other day in doses varying from 0.05 mg. to 2.5 mg. Following subsequent sensitization of both groups in the chamber for a total of six hours, re-exposure after an incubation period revealed no differences in anaphylactic responses between the pretreated and the six control animals. The same negative results followed re-exposure of the animals after a further daily injection of 2.5 mg. of histamine hydrochloride for a period of a week.

Equivocal percentage differences may be computed in favor of some protective effect from histamine in modifying respiratory anaphylaxis in the first four experiments; however, our clinical impression is that the

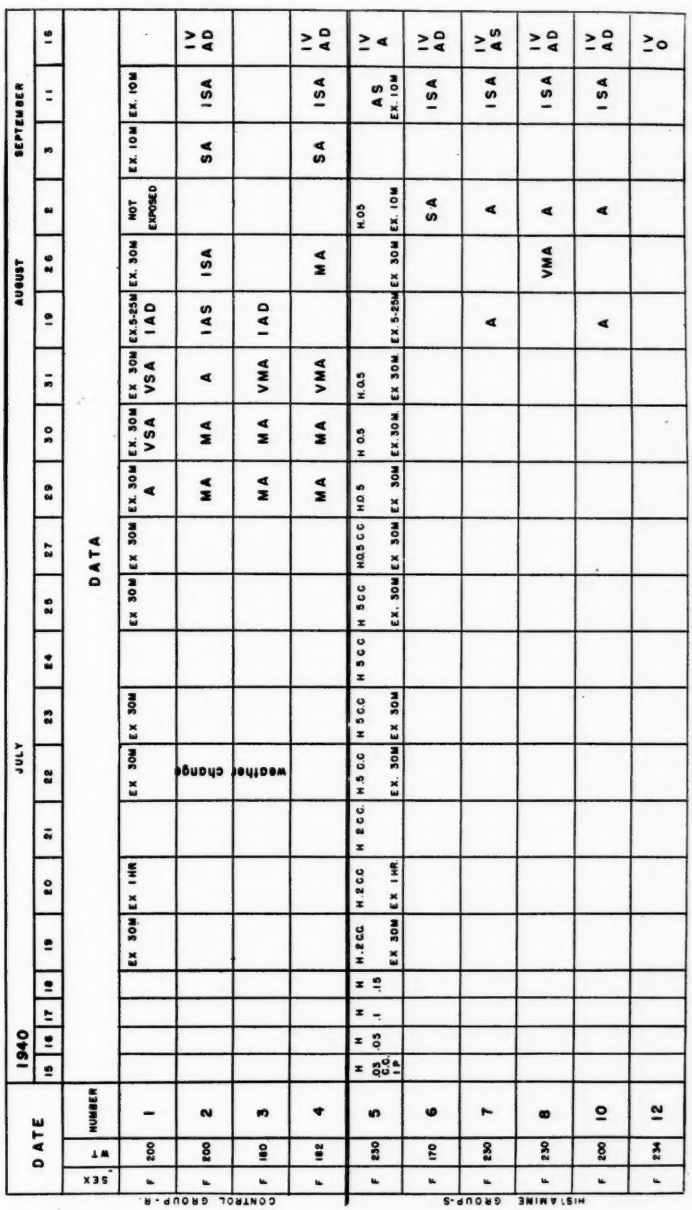


Fig. 3.—Day-to-day data on injections of histamine hydrochloride just prior to sensitizing and shock exposures. *M*, Minutes; *IAD*, immediate anaphylactic death.

injection of histamine in the dosage used by us, given either before or after sensitization had been effected, did not definitely modify the anaphylactic responses of guinea pigs sensitized and shocked by inhalation of an allergen.

Experiment 5.—In Fig. 5 a daily record is presented of the effect of administering acetylcholine, acetylcholine and histamine, and histamine alone over long periods to a group of guinea pigs sensitized as in previous experiments. Eight animals received 0.05 c.c. of a 1:1000 solution of acetylcholine bromide every second or third day for about five months.

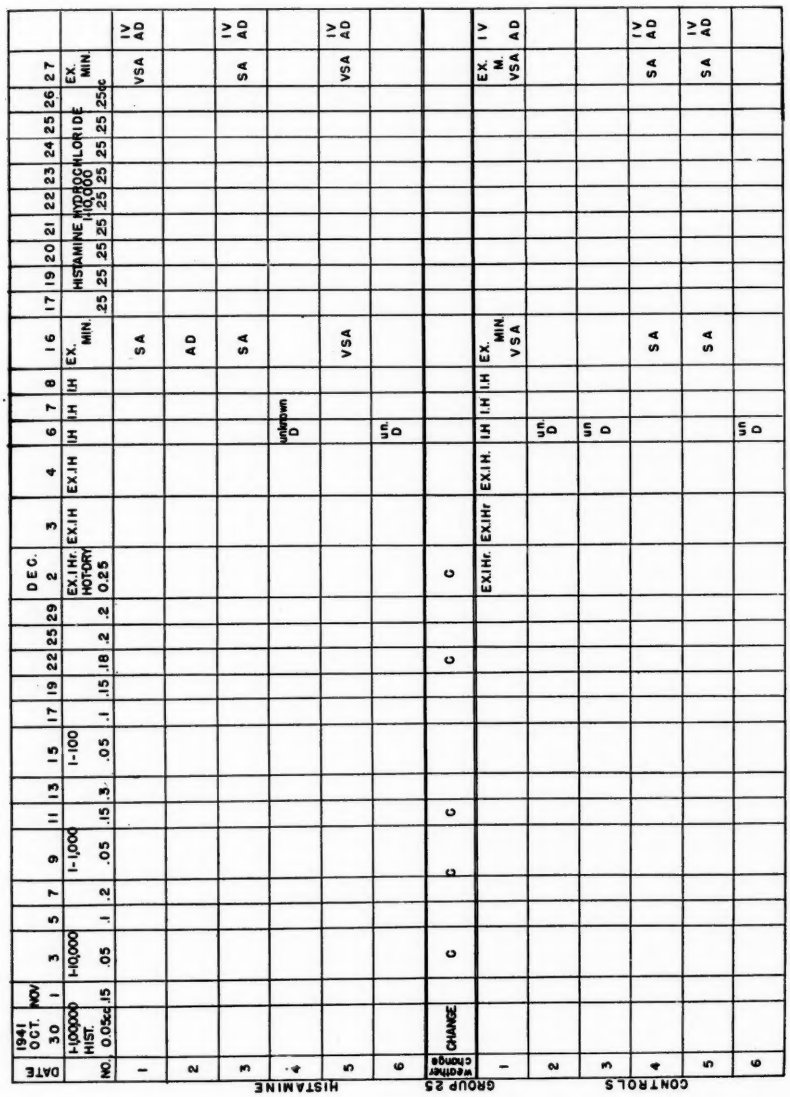


Fig. 4.—Day-to-day data showing injections of increasing amounts of histamine diphosphate prior to sensitizing exposure; days of exposure; shock reactions; histamine treatment after sensitization; further shock and final injection reactions. *unD*, Cause of death unknown.

Eight others received both 0.1 to 0.2 c.c. of histamine diphosphate in 1:1000 solution and also 0.05 c.c. of the 1:1000 acetylcholine solution. The dose of acetylcholine used was mildly toxic in some animals and caused death in two of the guinea pigs. Another group of eight animals was given histamine injections alone. All of the injections in the three

groups were made every other day before, during, and after sensitization, but on other than exposure days until after the fifth shock exposure. After the first shock exposure the animals were re-exposed approximately every week for three more months.

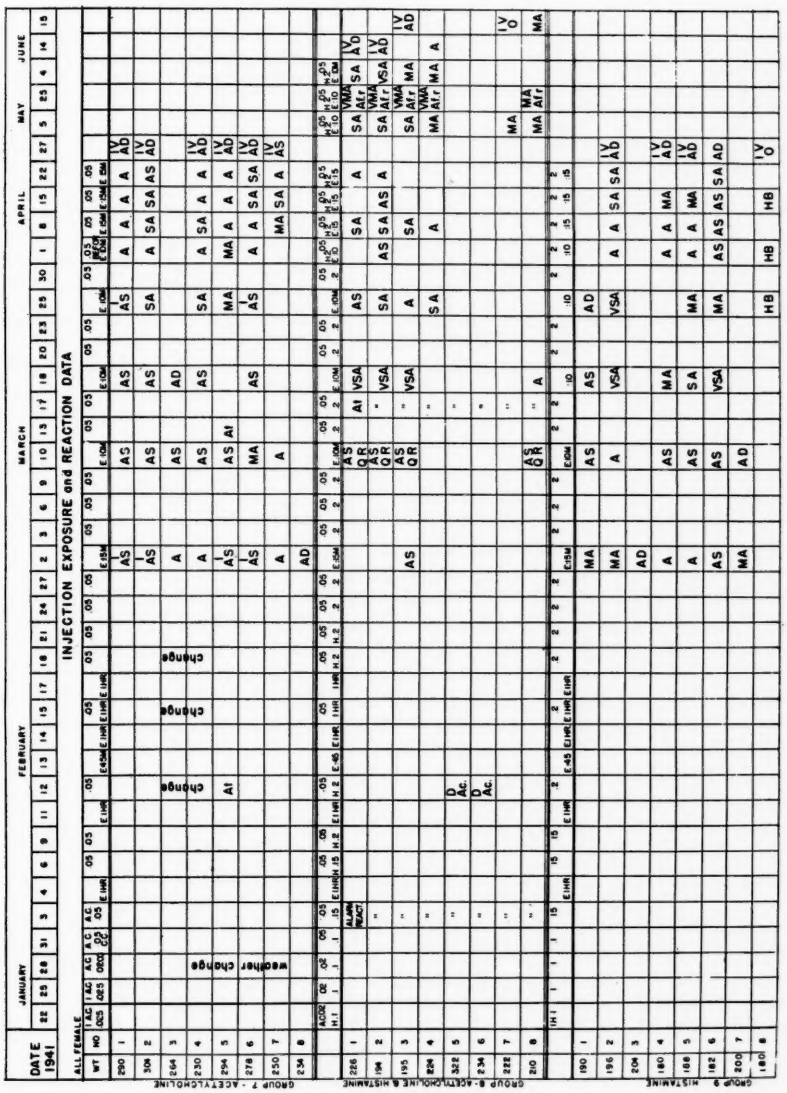


Fig. 5.—Chart showing data on three groups of guinea pigs treated simultaneously, one with acetylcholine, one with acetylcholine and histamine, and one with histamine, before, during, and after sensitization. *AC*, Acetylcholine bromide; *DAC*, death from acetylcholine; *Afr*, expiratory dyspnea after removal from chamber.

The guinea pigs which received the histamine injections alone showed responses similar to those already recorded. The animals treated with acetylcholine gave anaphylactic reactions on exposure to the dander as those treated with histamine. In the group where both acetylcholine and histamine were given there was a suggestion of delay in the appearance of clinical symptoms of anaphylaxis. However, continuation

of both drugs did not protect these animals from subsequent anaphylactic symptoms and death.

Experiment 5A.—We then sensitized eight animals by inhalation of horse dander for seven hours through a nine-day period. Four showed clinical evidence of anaphylaxis at this time. They were all then given almost daily injections of histamine and acetylcholine in very small increasing doses as shown in Table I. Thirty-five days after their last sensitizing exposure and after the twenty-four injections of histamine and acetylcholine they were exposed in the chamber to the dander in a hot, moist atmosphere (98° F. and 80 per cent relative humidity); two animals died an immediate anaphylactic death, two developed severe and one mild clinical symptoms, while three had no trouble. No apparent protection was afforded by the very small increasing doses of histamine and acetylcholine administered after sensitization.

Experiment 6.—Fig. 6 illustrates the effect of histaminase solution applied locally to the nasal membrane during inhalant sensitization. In the test group of seven animals we used 5 units of histaminase* dissolved in 2 c.c. of distilled water. Three drops of this solution were placed in the nares of each pig fifteen minutes before and every fifteen minutes during sensitization and shock exposures to the dry horse dander. Physiologic saline solution was dropped into the nares of eight control animals at identical times. Despite the brief four and one-half hours of dander inhalation, subsequent exposure in the chamber under dry, hot air conditions following the usual incubation period caused anaphylactic death in four of the seven histaminase pretreated animals and in five of eight control pigs. One week later another histaminase treated animal died on exposure to the inhalant. Two weeks later the remaining experimental animals were given slow intrajugular injections with 5 units of histaminase dissolved in 1.5 c.c. of normal saline. Anaphylactic death took place immediately after injection. Autopsy showed typical distention of lung alveoli as found in anaphylactic death rather than the toxic lesions seen frequently following histaminase injections. When histaminase was injected in the sensitized control animals, no symptoms occurred, and when these control animals were exposed to horse dander one and one-half hours later, clinical symptoms of anaphylaxis took place.

It had been noticed that on final treatment of the animals with histaminase solution intranasally, local signs of sensitivity were evident, notably rubbing of the nose, sneezing, and watery nasal discharge. These observations would suggest that histaminase intranasally acted as an allergen. The pigs became sensitive to both the histaminase and horse dander. Also of interest is the observation that the mere introduction of fluid media into the nasal membrane, whether it be histamin-

*Histaminase T 360-N was used. This is a Winthrop product prepared by the niphonoid process and containing 5 units per ampule.

TABLE I

DATES AND INJECTION DOSAGE OF HISTAMINE AND ACETYLCHOLINE USED IN THE EIGHT ANIMALS OF EXPERIMENT 5A PREVIOUSLY SENSITIZED BY INHALATION OF DRY HORSE DANDER

DATE (1942)	MG. OF HISTAMINE DIPHOSPHATE	MG. OF ACETYLCHOLINE BROMIDE
Feb. 2	0.0000001	0.001
3	0.00000015	0.0015
4	0.0000002	0.002
5	0.00000025	0.0025
6	0.0000003	0.003
7	0.0000003	0.003
8	0.0000005	0.005
9	0.0000005	0.005
10	0.000001	0.01
11	0.0000015	0.015
12	0.000002	0.02
14	0.0000025	0.02
15	0.0000025	0.025
17	0.000008	0.08
18	0.00001	0.10
19	0.000015	0.15
20	0.00002	0.20
21	0.00002	0.20
23	0.000025	0.25
24	0.00005	0.5
26	0.0001	1.0
March 1	0.00015	1.0
4	0.0002	1.0
6	0.0003	1.0
March 8	Re-exposed to horse dander	

ase solution or normal salt solution, is sufficient to lower the threshold for sensitization and shock from a dry allergen.

Experiment 7.—Two groups of animals were then sensitized with horse dander, thirty-five by the intraperitoneal route and six by inhalation. Eighteen of the intraperitoneally sensitized animals and the six sensitized by inhalation were given slow intrajugular injections of histaminase* in a dosage of 5 units in 1.5 c.c. of physiologic saline or distilled water. Ten of the animals died a toxic death several minutes to a few hours after injection. Autopsy showed the lungs filled with a faintly bloody serum. Subsequently the fourteen surviving sensitized guinea pigs which had received histaminase and those seventeen controls which had not were exposed to horse dander by inhalation in a dry, hot atmosphere. The time of these exposures after the injection of histaminase varied from fifteen minutes to five hours. Nine of the fourteen surviving animals had shown no toxic reactions to histaminase. Of these, 3 had no anaphylactic symptoms on exposure to dry horse dander, two died in anaphylactic shock, and four had severe expiratory dyspnea. Of the seventeen sensitized control animals which did not receive histaminase, thirteen showed definite clinical symptoms of anaphylaxis, two had no reactions, and two died in anaphylactic shock.

*See footnote on p. 452.

	DATE		AUGUST 41							SEPT	
			9	12	13	14	15	23	30	9	17
	SEX	WEIGHT	NUMBER	INJECTION EXPOSURE & REACTION DATA							
				4 UNITS HISTAMINASE T360-N IN 1/2 CC WATER - 3 GTTS IN NARES - 15 MIN	SAME	SAME	SAME	SAME	SAME	SAME	SAME	INJECTED I.V 4 UNITS T360-N IN 1.5 CC N-SALINE
				EXPOSURE 1 HR	E 1 HR	E 45 M	E 1 HR	E 45 M	E :10 M	E :10 M	E :10 M	
EXPERIMENTAL GROUP histamines	F	266	1						A	VSA	VSA	A D
	F	276	2						A D	weather change		
	F	306	3						A D			
	F	265	4						A D			
	F	234	5						MA	A D		
	F	220	6						A D			
	F	298	7						SA	VSA	VSA	AD
				N-SALINE DROPPED IN NARES - 15 MIN	SAME	SAME	SAME	SAME	SAME	SAME	SAME	INJ. I.V. 4 U. T360-N THEN EXPOSED 1.5 HR. LATER
				EXP	OSED A	S	AB	OVE				EX. :10 M.
CONTROL GROUP saline	F	262	1						A D			
	F	288	2						VSA	VSA	VSA	SA
	F	224	3						A D			
	F	280	4						A D			
	F	280	5						VSA	VSA	VSA	A
	F	235	6						A D			
	F	260	7						SA	VSA	VSA	A
	F	244	8						A D			

Fig. 6.—Data on guinea pigs treated during inhalation sensitization with histaminase solution and salt solution dropped into the nares. Four units of histaminase should read 5 units.

Our use of histaminase (niphonoid process), was perhaps unfortunate. We were unable to obtain the usual histaminase* which had always been used by other investigators. That used by us contained a larger number of units in a smaller quantity of material. Its physical form differed due to the niphonoid process of preparation. The action in vitro was

*Histaminase, Winthrop Company T 360.

comparable to that of the older histaminase. One unit neutralized 0.001 Gm. of histamine base when agitated at 37° C. for twenty-four hours.

We cannot explain the toxic reactions occurring in many of the injected pigs. The solution was given slowly in dilutions up to 3 c.c. of saline or distilled water but with no apparent differences. The fact that some of the animals showed no toxic reactions could mean a variability in the histaminase itself. When eight normal unsensitized guinea pigs of comparable weight were injected intrajugularly with histaminase of another list number, no clinical symptoms of toxicity occurred. Autopsy revealed no pathology.

DISCUSSION

The possible relationship between histamine shock and experimental anaphylaxis is still uncertain, and much recent literature has not clarified this problem. Most workers have found that histamine injections given during the incubation period, after parenteral sensitization, did not protect animals against anaphylactic shock. We believe, however, that no observations are on record in which histamine injections were given over a long period of time before, during, and after inhalant sensitization with a dry allergen.

Although we used both histamine diphosphate and the hydrochloride, and varied the dose, the time, and length of administration, we obtained the same negative results noted by other observers. Moreover, our method is to be regarded as somewhere intermediate between that of the sensitized uterine muscle in which Farmer[3] obtained positive results and the gross method of lethal shock used by other investigators.

In two experiments there was a suggestion that histamine pretreated animals may be more refractory to clinical and lethal symptoms. In this group a histamine solution prepared from stored crystals of histamine hydrochloride was injected in relatively large doses. This solution, made each day, was as lethal as the histamine diphosphate when tested on animals. The injections were made just prior to both the sensitizing and shock exposures. Whether or not there is a period in which refractoriness to sensitization and/or shock develops just after histamine injections cannot be proved, however, by the data of this experiment. Repeated injections of histamine just prior to inhalant sensitizing exposures might be more effective in modifying sensitization. Even under the most favorable experimental circumstances histamine appears to be ineffective in completely preventing sensitization and shock. If histamine is involved in the anaphylactic reaction, it must play a minor role or be only an end product.

The use of acetylcholine to prevent or alter anaphylactic shock was suggested not only by Pearson's clinical use of mecholyl to modify the reaction of wheat-sensitive patients, but also by the experiments of Campbell and Nicoll.[10] They found that rat uteri unaffected by or-

dinary doses of histamine responded to a substance released by sensitized guinea pig lung tissue during anaphylactic shock. They also found that the circular muscle of the uterus was more susceptible to acetylcholine than was the longitudinal muscle, but less susceptible to histamine. The possibility occurred to us that the combined effect of both acetylcholine and histamine on clinical anaphylaxis might be greater than either effect alone. At least, one might possibly anticipate a partial modification of the reaction. Furthermore it is barely possible that repeated injections of acetylcholine could stimulate more efficient cholinesterase action. This would be particularly important in guinea pigs since they are known to be the lowest in the scale of animals able to break down acetylcholine.[11] The slight delay of sensitization which was noted when using a combination of acetylcholine and histamine, however, was not definite enough to be very significant. Negative results were also obtained when very small increasing doses of histamine and acetylcholine were injected daily for a month in guinea pigs already sensitized by inhalation. In contrast to this, clinically, Farmer[12] and Dzsinich[13] reported improvement in patients with asthma after the injection of very small doses of histamine over long periods. It is realized that responses in guinea pigs are probably at least quantitatively different.

The use of histaminase to modify clinical and lethal anaphylaxis has been reported extensively in recent literature. Despite the positive protective effect reported by Karady and Browne,[4] other workers, notably Alexander and Bottom,[7] Youngner and his co-workers,[8] and Knoll[14] show experiments which do not support this view. Employment of histaminase gives rise to certain difficulties: (1) source, (2) time of injection, and (3) whether applied parenterally or locally. Because Williams, Alexander, and Kircher[15] found that histaminase given intravenously in rabbits is slow in inactivating histamine, we injected our histaminase solution as long as five hours before inhalant shock exposure. Even under variable conditions we noted no definite protective effect on clinical inhalant anaphylaxis. We did not try repeated intraperitoneal injections of histaminase because its antigenic properties might nonspecifically modify anaphylactic responses.

Furthermore, histaminase applied locally on the nasal membrane failed to protect the animals from inhalant anaphylaxis. These experimental observations do not support the clinical studies of Ertl,[16] who sprayed a solution of histaminase on the nasal membranes of hay fever patients and concluded that histaminase protected them for long periods of time. It has already been observed by Ratner and his associates[17] that a liquid allergen acts as a more potent material for inhalant sensitization than a dry one. The histaminase and physiologic salt solutions were evidently ideal in converting the dry horse dander into a more potent sensitizing agent. A note of warning could be taken here

concerning the use of solutions applied to man's nasal membranes when there is the possibility of sensitization in a susceptible individual.

Although negative results are common in studies aimed at finding key substances involved in the anaphylactic reaction, findings such as are described by Campbell and Nicoll urge one on to further work.

SUMMARY

1. The air-conditioned chamber has proved a valuable method of studying the preventive or modifying effect of various pharmacologic agents on inhalation sensitization.

2. Histamine injected before, during, and after sensitization, under the conditions of our experiments, did not prevent clinical or lethal anaphylactic shock.

3. Histamine injections in large doses, given just prior to each exposure of the animals to the sensitizing allergen and just before subsequent shock exposure, seemed to delay the appearance and reduced the violence of clinical symptoms of anaphylaxis in a small group of animals.

4. Acetylcholine injections given before, during, and after sensitization did not appear to modify the course of anaphylactic responses. There is slight suggestive evidence that acetylcholine and histamine injected within a short period of one another, at the same time intervals during sensitization as the acetylcholine group, delayed the appearance of clinical anaphylaxis.

5. Histaminase solution given intranasally during inhalation sensitization and shock not only did not protect animals against clinical anaphylaxis but actually augmented their symptoms. Histaminase here also acted as a sensitizing allergen. It was observed that the application of a watery solution to the nasal membranes may lower the threshold of sensitization to a dry allergen.

6. Histaminase injected intravenously in animals sensitized either by inhalation or peritoneal injection did not protect them against anaphylactic symptoms following the inhalation of horse dander.

We are grateful to Mr. Louis Pingree for his assistance.

REFERENCES

1. Courtright, L. J., Hurwitz, S. H., and Courtright, A. B.: J. ALLERGY **13**: 271, 1942.
2. Fühner, H.: München. med. Wchnschr. **59**: 852, 1912.
3. Farmer, L.: J. Immunol. **36**: 37 and **37**: 321, 1939.
4. Karady, S., and Browne, J. S. L.: J. Immunol. **37**: 463, 1939.
5. Barlow, O. W., and Homburger, E.: J. ALLERGY **12**: 346, 1941.
6. Neely, F. L.: J. Lab. & Clin. Med. **27**: 319, 1941.
7. Alexander, H. L., and Bottom, D.: J. Immunol. **39**: 457, 1940.
8. Youngner, J. S., Freedman, S. I., and Nungester, W. J.: Proc. Soc. Exper. Biol. & Med. **46**: 187, 1941.
9. Pearson, E. F.: Ann. Int. Med. **13**: 2241, 1940.

10. Campbell, D., and Nicoll, P.: J. Immunol. **39**: 103, 1940.
11. Cannon, W. B., and Rosenbleuth, A.: Autonomic Neuro Effector Systems, New York, 1937, The Macmillan Co.
12. Farmer, L.: New York Acad. Med. Bull. **16**: 618, 1940.
13. Dzsinich, A.: Klin. Wchnschr. **14**: 1612, 1935.
14. Knoll, A. F.: Proc. Soc. Exper. Biol. & Med. **45**: 607, 1940.
15. Williams, R., Alexander, H. L., and Kircher, T.: J. ALLERGY **12**: 359, 1941.
16. Ertl, E.: Wien. klin. Wchnschr. **52**: 643, 1939.
17. Ratner, B., Jackson, H. C., and Gruehl, H. L.: Am. J. Dis. Child. **34**: 23, 1927.
18. Ratner, B., Jackson, H. C., and Gruehl, H. L.: Am. J. Dis. Child. **58**: 699, 1939.

ACTIVE SENSITIZATION IN HUMAN BEINGS WITH TRICHINA ANTIGEN

BESSIE BARON, B.A., AND MATTHEW BRUNNER, M.D.
BROOKLYN, N. Y.

FÜLLEBORN and Kikuth[1] observed that the injection of Ascaris extract into a nonsensitive person induced a skin hypersensitiveness. Coca[2] had a similar experience. Brunner[3, 4] found that it was possible to sensitize a large percentage of humans to Ascaris antigen by several subcutaneous injections of the extract. These positive cutaneous reactions could be transferred to the skins of normal individuals by the Prausnitz-Küstner technique.[5]

The present study was undertaken for the purpose of determining whether the skin test doses of Trichina antigen, which are used as a diagnostic aid in detecting Trichinella infestation,[6-9] can sensitize the patients to this antigen. If this was possible, it seemed desirable to study the nature of the immunologic mechanism involved. Because of the group relationship of *Trichinella spiralis* and *Ascaris lumbricoides,* it also seemed advisable to study the relationship of the sensitivities induced by these two antigens.

METHOD

Rabbits were infested with the larvae of *Trichinella spiralis,* and adult worms were recovered according to the technique suggested by McCoy and his associates.[6] Since it was difficult to obtain a large quantity of Trichina antigen at one time, three different Trichina extracts, No. 4, No. 5, and No. 9 were prepared during the course of these investigations. Extracts No. 4 and No. 5 were prepared in the following manner. Trichinae which were obtained from digested muscle of infested rabbits were washed with saline. They were triturated with a small quantity of sand in a mortar. A few milliliters of buffered saline were added to this material. This was then passed through a Seitz filter and was tested for sterility. These extracts were used in undiluted form. Because the amount of extract obtained was very small, standardization was not attempted. Trichina antigen No. 9 was prepared by washing the parasites in physiologic saline and drying them on a watch crystal which was kept in the incubator at 37° C. The Trichinae were then ground to a fine powder. One gram of this powder was extracted with 20 ml. of buffered saline and was placed in the incubator at 37° C.

From the Department of Allergy, Jewish Hospital of Brooklyn.

Read at the Semiannual Meeting, Division of Allergy, Jewish Hospital of Brooklyn, Nov. 21, 1938, and abstracted in the J. ALLERGY **10:** 183, 1939.

for thirty-six hours. The solution was then passed through a Seitz filter and was tested for sterility. This extract contained 2.35 mg. of nitrogen per milliliter. It was used in a dilution of 0.1 mg. of nitrogen per milliliter for these experiments.

This study was made on three series of subjects, each consisting of six atopic patients varying from 4 to 44 years of age. These patients were attending the allergy clinic for the treatment of various allergic illnesses. The atopic nature of the subjects probably did not influence the results obtained, for in our previous experiments with Ascaris, no greater tendency to sensitization with this antigen was found in atopic than in nonatopic individuals.[3, 4]

Subjects were first tested intracutaneously with 0.01 ml. of Trichina antigen No. 9 (0.1 mg. of nitrogen per milliliter), and only those giving negative reactions were used. Injections of 0.1 ml. were then given at intervals of from one to two weeks over a period which varied from four to twenty weeks. Skin reactions were read within fifteen minutes after testing.

With the development of hypersensitiveness, a positive reaction resulted from the intracutaneous test. This consisted of an erythema, associated with an itch, which appeared about five minutes after the injection. Wheal formation then followed. Wheals which were 0.8 cm. in diameter were read as 0±, 1 cm. in diameter as ±, and 1.2 cm. or over as +. Erythemas which were 2 cm. in diameter were noted as ±, 3 cm. as +, 3.5 cm. as + ±, 4 cm. as + +, and 4.5 cm. as + + ±.

In Series 1, six patients from 12 to 28 years of age were treated with Trichina antigen No. 4 (Table I). They received sensitizing injections of 0.1 ml. of undiluted antigen over a period of from four to ten weeks. Positive reactions consisting of at least one-plus erythemas and wheals were obtained in the patients in Cases 1 and 2 with the third sensitizing dose, and in the patient in Case 3 with the fifth sensitizing dose. Cutaneous tests were repeated in these patients to check the results. The reactions in three patients, Cases 4, 5, and 6, remained negative or doubtful after six injections.

In Series 2, six children from 4 to 12 years of age were treated with Trichina antigen No. 5 (Table II). Sensitizing injections consisted of 0.1 ml. of antigen and were given intracutaneously for a period of from six to nine weeks. A positive cutaneous reaction was obtained in the child in Case 8 with the sixth sensitizing dose, in the child in Case 10 with the seventh, and in the patient in Case 7 with the ninth. Doubtful reactions were obtained with the fourth injection in two children, Cases 9 and 12. Of these, one continued to show a doubtful reaction even after the eighth sensitizing dose; in the other, the reaction became negative with the sixth injection. The child in Case 11 showed no definite positive reactions after eight sensitizing doses.

In Series 3, the six patients ranged from 14 to 44 years of age. Sensitizing doses of 0.1 ml. of Trichina antigen No. 9, containing 0.1 mg. of nitrogen per milliliter, were administered intracutaneously over a period of from twelve to twenty weeks. Positive reactions were obtained with the fourth injection in the patient in Case 18, with the fifth in the patients in Cases 13 and 15, and with the eighth in the patient in Case 14.

TABLE I

ACTIVE SENSITIZATION OF ATOPIC SUBJECTS WITH TRICHINA ANTIGEN NO. 4 (SERIES 1)

CASE NO.	AGE (YR.)	PERIOD OF INJECTIONS (WK.)	INITIAL TEST WITH TRICHINA NO. 4* 0.01 ML. INTRACUTANEOUSLY; UNDILUTED		SENSITIZING INJECTIONS WITH 0.1 ML. INTRACUTANEOUSLY; UNDILUTED					
					1	2	3	4	5	6
1	14	4	Wheal	0	0	±	+	+		
			Erythema	0	0	±	+±	±		
2	14	7	Wheal	0	0	±	+	+	+	
			Erythema	0	0	0±	±	±	+	
3	12	10	Wheal	0	0	0±	0	0	+	+
			Erythema	0	0	±	0	0	+	+
4	28	5	Wheal	0	0	0	0	0	0	0
			Erythema	0	0	0	0	0	0	0
5	13	5	Wheal	0	0	0	0±	0±	0±	0±
			Erythema	0	0	0	±	±	±	0±
6	13	5	Wheal	0	0	0±	0	0	0	0
			Erythema	0	0	0+	0	0	0	0

*Nitrogen content undetermined.

Wheal

0± 0.8 cm in diameter
± 1.0 cm. in diameter
+ 1.2 cm. or over in diameter

Erythema

0± Faint blush
± 2.0 cm. in diameter
+ 3.0 cm. in diameter
+± 3.5 cm. in diameter
++ 4.0 cm. in diameter
++± 4.5 cm. in diameter

These results were confirmed on subsequent tests. In the patient in Case 17, a doubtful reaction was obtained with the ninth and eleventh sensitizing doses. The patient in Case 16 failed to give a definite positive reaction by the eleventh injection.

In some instances, as in the patient in Case 12 (Table II) and in the patient in Case 17 (Table III), ± wheals were elicited which did not reappear when subsequent sensitizing doses were administered. In these two patients, wheals of a one-plus intensity were never obtained, and the results were considered negative.

In summarizing these 18 cases, ten (56 per cent) of the patients revealed the presence of induced sensitivity as indicated by definite wheal and erythema formation. Of these, positive reactions (at least one-plus intensity) occurred with the third sensitizing dose in two patients, with the fourth in one, with the fifth in three, with the sixth in one, with the seventh in one, with the eighth in one, and with the ninth in one. In two patients (11 per cent) doubtful reactions, never more than a ± in intensity, were obtained.

TABLE II

ACTIVE SENSITIZATION OF ATOPIC SUBJECTS WITH TRICHINA ANTIGEN NO. 5 (SERIES 2)

CASE NO.	AGE (YR.)	PERIOD OF INJECTIONS (WK.)	INITIAL TEST WITH TRICHINA NO. 5* 0.01 ML. INTRACUTANEOUSLY; UNDILUTED		SENSITIZING INJECTIONS WITH 0.1 ML. INTRACUTANEOUSLY; UNDILUTED								
					1	2	3	4	5	6	7	8	9
7	8	8	Wheal	0	0±	0±	0±	0±	±	0±	±	±	+
			Erythema	0	0±	0±	0±	0±	±	0±	±	±	±
8	9	8	Wheal	0	0	0±	0±	0±	±	+			
			Erythema	0	0	0±	0±	0±	±	+			
9	6	8	Wheal	0	0	0	0	±	±	±	±	±	
			Erythema	0	0	0	0	±	0±	0±	±	±	
10	12	7	Wheal	0	0	0	0	0±	0±	±	+	+	
			Erythema	0	0	0	0	0±	0±	±	+±	++	
11	8	7	Wheal	0	0	0	0	0	0	0±	0±	0±	
			Erythema	0	0	0	0	0	0	±	0±	±	
12	4	7	Wheal	0	0	0	0±	±	±	0	0		
			Erythema	0	0	0	0	0±	0±	0	0		

*See footnote to Table I.

Passive Transfer Studies With Trichina Sera.—An investigation was then carried out to determine whether it was possible to transfer these induced positive cutaneous reactions to the normal skin according to the Prausnitz-Küstner technique. The relationship between the Trichina and Ascaris antigens was also studied in this manner.

Blood was taken from the subjects when definite signs of cutaneous sensitivity developed. The blood was centrifuged. The serum was pipetted off and passed through a Seitz filter. It was placed in tubes and kept in the refrigerator without preservative. The subjects used for passive transfer tests were normal nonatopic individuals who gave negative reactions to intracutaneous tests. For sensitization, 0.05 ml. of undiluted serum was injected intracutaneously at each site. Several sites were prepared on each arm. They were tested intracutaneously from three to seven days after sensitization. Control tests were always made on the normal skin of the subject adjacent to the sensitized sites. Ascaris extract in a dilution of 0.1 mg. of nitrogen per milliliter and Trichina antigen undiluted, or in dilutions of 1 or 0.10 mg. of nitrogen per milliliter were used for testing. Reactions were read about twenty minutes after the test was performed.

The passive transfer studies were done with two types of sensitizing sera. Comparative cutaneous tests with Trichina and Ascaris antigens were made on sites passively sensitized with sera obtained from the patients in whom Trichina or Ascaris hypersensitiveness had been induced. They were also performed with sera obtained from patients who were sensitive to Ascaris antigen as a result of infestation with these parasites.

TABLE III

ACTIVE SENSITIZATION OF ATOPIC SUBJECTS WITH TRICHINA ANTIGEN NO. 9 (SERIES 3)

CASE NO.	AGE (YR.)	PERIOD OF INJECTIONS (WK.)	INITIAL TEST WITH TRICHINA NO. 9* 0.01 ML. INTRACUTANEOUSLY; DILUTION 0.1 MG. N/ ML.		SENSITIZING INJECTIONS WITH 0.1 ML. INTRACUTANEOUSLY; DILUTION 0.1 MG. N/ ML.										
					1	2	3	4	5	6	7	8	9	10	11
13	14	20	Wheal	0	0	0	±	0±	+	±	+	+	+	+	+
			Erythema	0	0	0±	+±	0±	+	++	++	++	++	++	++±
14	32	20	Wheal	0	0	0	0	±	±	±	±	+	+	+	+
			Erythema	0	0	0	0	0±	0	0±	+±	+±	+±	++	++
15	44	20	Wheal	0	0	0	0	±	+	±	+	+	±	+	+
			Erythema	0	0	0	0	0±	+±	±	++	±	0±	0±	0±
16	20	12	Wheal	0	0	0	0	0	0	0	0±	0±	0±	0±	0±
			Erythema	0	0	0	0	0	0	0	0±	0±	0±	0±	0±
17	25	12	Wheal	0	0	0	0	0±	0	0	0	0	±	0	±
			Erythema	0	0	0	0	0±	0	0	0	0	±	0	±
18	26	12	Wheal	0	0	0	0	+							
			Erythema	0	0	0	0	+							

*See footnote to Table I.

TABLE IV

COMPARATIVE PASSIVE TRANSFER STUDIES WITH TRICHINA AND ASCARIS ANTIGENS ON TRICHINA-SENSITIVE SERA

CASE NO.	NATURE OF TRICHINA SENSITIVITY	NUMBER OF TRICHINA TRANSFER TESTS DONE	RESULTS OF TESTS WITH TRICHINA ANTIGEN				NUMBER OF ASCARIS TRANSFER TESTS DONE	RESULTS OF TESTS WITH ASCARIS ANTIGEN			
			0	+	++	+++		0	+	++	+++
1	Artificially induced	7	2	4		1	1			1	
2	Artificially induced	4	1	1	2		2		2		
3	Artificially induced	4	1	2	1		2		2		
4	Artificially induced	6		5	1		4	2	2		
5	Artificially induced	5	1	3	1		3	2	1		
6	Artificially induced	4		2	1	1	3	1			2
7	Artificially induced	4	2	2			2	2			
8	Artificially induced	8	3	5							
9	Artificially induced	4	1	2	1						
10	Artificially induced	3		3							
11	Natural	5	1	4							
12	Natural	2		2							
13	Natural	1	1								
Totals		57	13	35	7	2	17	7	7	1	2
Per cent			23	61	12	4		41	41	6	12

It was possible to obtain sera from only nine of the eighteen patients actively sensitized with Trichina antigen (Cases 1 to 5 and 7 to 10 inclusive; Table IV). All of these were tested with Trichina, but only six were tested with Ascaris. In addition, passive transfer tests for Trichina were done on sera obtained from three hospitalized patients, Cases 11, 12, and 13 (Table IV), who had been admitted with a doubtful clinical diagnosis of trichinosis. Transfer tests for both antigens were also done with the serum of one of us (B. B.) (Case 6, Table IV) who had become actively sensitized to Trichina antigen as the result of contact with the parasites during the process of preparing extracts of them. In this case there was no history of infestation with parasites, and previous intracutaneous test with Ascaris and Trichina antigens had been negative. After the completion of Trichina extract No. 9, a preliminary test on this subject yielded a marked reaction. It is interesting to note that the transfers obtained with this patient's serum were stronger than those obtained with the sera of the actively sensitized patients.

The results of fifty-seven transfer tests done on Trichina sera with Trichina antigen are summarized in Table IV. Thirteen, or 23 per cent, were negative; 35, or 61 per cent, were weakly positive (+); seven, or 12 per cent, were definitely positive (++); and two, or 4 per cent, were strongly positive (+++). Among the seventeen transfer tests done on these same sera with Ascaris antigen, the following results were obtained: Seven, or 41 per cent, were negative; seven, or 41 per cent, were weakly positive (+); one, or 6 per cent, was definitely positive

(++); and two, or 12 per cent, were strongly positive (+++). These results indicate that *Trichinella spiralis* and *Ascaris lumbricoides* possess a common antigen. However, on sites passively sensitized with Trichina serum, the homologous antigen gave stronger reactions than the heterologous one.

TABLE V

COMPARATIVE PASSIVE TRANSFER STUDIES WITH TRICHINA AND ASCARIS ANTIGENS ON ASCARIS-SENSITIVE SERA

CASE NO.	NATURE OF ASCARIS SENSITIVITY	NUMBER OF ASCARIS TRANSFER TESTS DONE	RESULTS OF TESTS WITH ASCARIS ANTIGEN					NUMBER OF TRICHINA TRANSFER TESTS DONE	RESULTS OF TESTS WITH TRACHINA ANTIGEN				
			0	+	++	+++	++++		0	+	++	+++	++++
1	Artificially Induced	2	1	1				2	1	1			
2	Artificially Induced	2		1	1			2	2				
3	Artificially Induced	1					1	1	1				
4	Artificially Induced	2		1	1								
5	Artificially Induced	2				2							
6	Artificially Induced	2				2							
7	Artificially Induced	2				2							
8	Natural	1					1	4	3		1		
9	Natural	3				2	1	1	1				
Totals		17	1	3	2	8	3	10	8	1	1		
Per cent			6	18	12	47	18		80	10	10		

Passive Transfer Studies With Ascaris Serum.—It was also possible at this time to obtain sera from seven patients actively sensitized to Ascaris antigen, but comparative tests with Trichina and Ascaris antigens were done on only three (Table V). Comparative tests were also done with sera from two patients, Cases 8 and 9, obtained from Ascaris-infested patients.

The results of seventeen positive transfer tests done with Ascaris antigen on the nine Ascaris sera are summarized in Table V. One, or 6 per cent, was negative; three, or 18 per cent, were weakly positive (+); two, or 12 per cent, were definitely positive (++); eight, or 47 per cent, were strongly positive (+++); and three, or 18 per cent, were markedly positive (++++). Among the ten passive transfer tests done on these same sera with Trichina antigen, the following results were obtained: Eight, or 80 per cent, were negative; one, or 10 per cent, was weakly positive (+); and one, or 10 per cent, was definitely positive (++). With these sera also, homologous antigen gave stronger reactions than the heterologous one. The results obtained suggested the existence of a common antigen in Trichina and Ascaris extracts.

SUMMARY

1. Skin test doses of Trichina antigen may sensitize the skins of normal individuals.

2. Definite marked hypersensitization developed after three to five sensitizing injections in six of eighteen patients (33.3 per cent).

3. Ten of eighteen patients (56 per cent) showed definite evidence of sensitivity by the ninth test dose.

4. The cutaneous reaction in sensitivity to *Trichinella spiralis* is mediated by the atopic reagin and is transferable to the normal skin.

5. A common antigen exists in Ascaris and Trichina antigens.

6. The common antigen is probably stronger in the Ascaris than in the Trichina extract, even though the Trichina antigen transfers better on Trichina sera.

7. From a practical point of view, it is well to remember that the diagnostic value of the Trichina tests diminishes with repeated intracutaneous injections.

REFERENCES

1. Fülleborn, F., and Kikuth, W.: Klin. Wchnschr. **8**: 1988, 1929.
2. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., 1931, Charles C Thomas.
3. Brunner, M.: J. ALLERGY **5**: 257, 1934.
4. Brunner, M.: Unpublished experiments.
5. Prausnitz, C., and Küstner, H.: Centralbl. f. Bakt. **86**: 160, 1921.
6. McCoy, O. R., Miller, J. J., and Friedlander, R. D.: J. Immunol. **24**: 1, 1933.
7. Augustine, D. L., and Theiler, H.: J. Parasitol. **24**: 60, 1932.
8. Bachman, G. W.: J. Prev. Med. **3**: 465, 1929.
9. Kaljus, W. A.: Puerto Rico J. Pub. Health & Trop. Med. **11**: 768, 1935-1936

EXPERIMENTAL REPRODUCTION OF GASTRIC ALLERGY IN HUMAN BEINGS WITH CONTROLLED OBSERVATIONS ON THE MUCOSA

H. M. Pollard, M.D., Ann Arbor, Mich., and George J. Stuart, M.D., Washington, D. C.

THE susceptibility of the gastrointestinal tract to analphylactic changes was first appreciated after the basic experiments of Schittenhelm and Weichardt[1,2] in 1910. These investigators were able to produce severe intestinal symptoms in sensitized dogs by reinjection of egg protein. They observed numerous miliary hemorrhages in the entire gastrointestinal tract involving both the mucosa and submucosa. In the stomach, hemorrhagic areas were localized to the pyloric region, and the fundus remained free of any abnormal change. Since this description by Schittenhelm and Weichardt there have been numerous descriptions and observations in which specific allergens have been found to produce allergic alterations in the gastrointestinal tract and which bring about well-defined clinical manifestations.

Other animal experimentations have been performed by various investigators such as Demel,[3] Shapiro and Ivy,[4] Alessio,[5] Vallone,[6] Culmone,[7] and Guerrisi[8] for the specific purpose of determining the relationship between allergy of the stomach and the production of gastric ulcer. These various authors sensitized rabbits, guinea pigs, and dogs with horse serum and observed after intravenous reinjection or after reinjection in the stomach wall itself an Arthus phenomenon with hyperemia, hemorrhagic infiltrations, and erosions. In none of these experiments was there any relationship of allergy to the cause of chronic stomach ulcer, since after such a short time the lesions spontaneously regressed. In these and in other investigations (Rössle,[9] Knepper,[10] Kaiserling and Oehse[11]) no observations were made concerning the secretory functions of the stomach or of histologic changes except those in which local anaphylaxis was induced.

Afendulis and Gulzow[12] studied the allergic manifestations in the stomachs of six dogs by obtaining direct observation of the stomach mucosa with the gastroscope, by following the secretory changes, and by observing the histologic characteristics. A control period of several weeks was utilized in order to make observations under normal conditions before sensitizing the animal. The animals were then sensitized in two-day intervals by three injections subcutaneously of 5 c.c. of nor-

From the Department of Internal Medicine, University Hospital, University of Michigan.

This project was aided in part by a grant from the Horace H. Rackham School of Graduate Studies.

mal horse serum. Eighteen to twenty-eight days after the last injection, and after normal conditions had returned, anaphylactic shock was produced by intravenous reinjection of the same antigen. Their results in general were similar to those described by Schittenhelm and Weichardt.[1] About one-half hour after the reinjection, the dogs had allergic enteritis with diarrhea and edema of the anus. Gastroscopically the stomachs of these dogs showed edematous swelling and increased redness of the antrum mucous membrane with increased broadening of the rugal folds. The stomach was spastic, especially the pyloric portion. The spastic pylorus in these dogs showed no movement. A few hours later, however, the changes spread to the body of the stomach, and in the course of twenty-four hours they developed a picture of pangastritis with marked edematous swelling in the body and antrum, which showed a mottling of various size and form with extensive bleeding and hemorrhagic erosion. These changes were most pronounced in the antrum, although in all cases the corpus, and in some instances the fornix, was also involved. After two to four days there was a regression of these changes, and in ten to fourteen days the stomachs looked completely normal again.

The fractionated gastric secretion in all the dogs sensitized by Afendulis and Gulzow[12] showed a hyperacidity and increased secretion.

There have been a few direct observations of the human stomach mucosa made during an allergic reaction involving the intestinal tract. Chevallier,[13] and later Paviot and Chevallier,[14] described the gastroscopic appearance of allergic alterations in the stomach. They conclude that transient edema of the antrum is the essential feature noticed in the typical patient. One of their patients showed the characteristic edema of Quincke. The edema disappeared in twenty-four to forty-eight hours with improvement of the clinical picture. In two of their patients the radiologist was able to observe transient changes in the mucosa in which the rugal folds changed from simple irregularities to spongy masses principally localized to the antral pyloric region. The emptying time was delayed which they considered extremely important. Chevallier[13] found that the pseudoneoplastic areas represented by the x-ray were in reality angioneurotic edema. Gastroscopically the mucosa is slightly brilliant and devoid of exudates and some areas resemble small liverworts. Moutier[15] in very general terms reports that what is true for allergic reactions of the skin is certainly true for the stomach.

Lundbaek[16] in 1939 at Copenhagen reported the gastroscopic observation in one patient with angioneurotic edema accompanied by gastrointestinal symptoms, in which the vomiting was controlled by adrenalin. The gastroscopic findings were as follows: The mucous membrane appeared to be succulent, the lumen was decreased, and the gastric folds were increased in width and circumference and were closer together. The greatest change appeared in the lesser curvature which demonstrated a lumpy contour. The color was a deeper red than normal, but there

was no increase in the shiny appearance. There were no signs of proliferation, atrophy, or mucus. Repeat gastroscopy was done three days later after calcium had been given intravenously, and there was complete recovery of the gastric mucosa to normal.

Gutzeit and Teitge[21] found gastroscopically in allergic individuals, particularly those with bronchial asthma, chiefly an atrophic gastritis, occasionally hypertrophic.

Wiedemann[17] and Rowe[18] found pylorospasm with increased peristalsis and delayed emptying time in the x-rays of individuals who had gastrointestinal allergy. They explained this on the basis of a localized or generalized stomach edema with spasm of the smooth muscle. Similar findings were made by Eyermann[19] and by Friedenwald and Feldmann.[20]

Afendulis and Gulzow[12] conclude from their experimental study on animals and the work of others that there is such a clinical entity as allergic gastritis. This process is distinguished from the acute gastritis of nonallergic individuals in that in the allergic "the course of the process is enormously increased and the intensity is much greater" (Gerlach[22]). They differentiate two different processes: (1) An allergic gastritis in human beings which occurs as a hyperergic reaction in the stomach. To this group belongs the *gastropathia allergica*, described as a clinical entity. (2) An allergic gastritis may occur in diseases of allergic etiology such as bronchial asthma. This occurs by the liberation of histamine in the stomach. They believe that the process described by Gutzeit and Teitge[21] of atrophic gastritis in allergic individuals with bronchial asthma is explained by the above. Also it explains the findings by Voss and Voss[23] in acute and allergic skin conditions in which they were able to find a hypersecretion, and in chronic allergic skin conditions, a hypo- or even an anacidity.

Every episode of an allergic nature causes a new stimulus on the stomach with a consequence that it serves to bring about a gastritis, which, with repeated insults of an acute episode, may result in permanent damage and may lead to chronic gastritis. The end result is an atrophy of the mucous membrane caused by chronic stimulation.

Afendulis and Gulzow[12] maintain that their experimental results on dogs coincide with the observations made by Chevallier[13] and Moutier[15] on human beings in acute gastrointestinal allergy, with the exception that their changes persisted much longer and that one could not differentiate gastroscopically between gastrointestinal allergy and acute gastritis in dogs. Apparently the process which they produced in the dogs was much more severe, and lasted longer.

Repeated acute gastritis in human beings can finally lead to chronic inflammatory changes in the stomach. Therefore in many obscure stomach complaints in which there are chronic or inflammatory changes in the mucosa, allergy should be considered as a possible etiology.

EXPERIMENTAL

In order to study the effect on the gastric mucosa of the ingestion of a specific allergen, we observed the gastric mucosal changes in a group of thirteen patients. Six of the selected cases for Group I (Cases 1 to 6) presented clear-cut clinical evidence of gastrointestinal allergy produced by a specific food but without manifestation of allergy elsewhere in the body. Four additional cases in Group II (Cases 7, 8, 9, and 10) were being treated in the hospital for bronchial asthma which could be precipitated by a specific food. These four patients did not have any gastrointestinal symptoms. The patient in Case 11 (Group III) was being treated for asthma not due to any food and with no gastrointestinal complaints. The patients in Cases 12 and 13 (Group IV) were selected as controls since they were without any personal or family history of allergy or of gastrointestinal complaints. These patients were all completely investigated in the division of allergy by one of us (G. J. S.) and were given complete skin tests. Those with gastrointestinal allergy were clinically proved allergic by the ingestion test. The gastroscopic observations were made in every instance by one observer (H. M. P.). We followed the suggestion made by Moutier[15] in eliminating atropine and adrenalin from the medication prior to the gastroscopic observation.

The routine established for the examination was to fast the patient for twelve hours, following which a control observation of the gastric mucosa was made. The specific antigen was then placed in the stomach and allowed to remain for thirty to sixty minutes and until some form of the original stomach complaint was reproduced. The contents of the stomach were then emptied, and a second observation of the gastric mucosa was made by means of the gastroscope.

RESULTS

One patient studied according to the above program was a colored female, aged 22 years. She gave a history of periodic episodes of abdominal discomfort and cramps for which she had been treated by an ulcer diet. Each time she became worse on the diet and had hemorrhaged profusely from the stomach on three occasions, once while in the hospital. Complete gastrointestinal x-rays had consistently been negative. Suspecting eggs as being the offending allergen, we subjected her to the above-mentioned program. The control observation of her gastric mucosa showed no definite abnormality. Following this a soft-boiled egg was placed in her stomach and within fifteen minutes she developed her customary upper abdominal cramplike discomfort. At the end of thirty minutes the stomach was emptied of its contents and the gastroscope was again inserted. A striking change had taken place. The color of the gastric mucosa was a dull pinkish orange, and there was complete absence of highlights. The mucosa had developed a blotchy, pseudopolypoid character to it, and the rugal folds had become thickened and

almost rigid. Several submucosal bleeding points were observed but no actual bleeding. A thick gray mucous was adherent to the mucosa in several areas. The changes described above were scattered throughout the entire gastric mucosa. After removing the gastroscope her symptoms were improved with a hypodermic of adrenalin and subsequently she was completely relieved of her symptoms by eliminating eggs from her diet but with no other restrictions.

Fig. 1 (Case 3).—*A*, before; *B*, after. This patient was clinically sensitive to salmon. Salmon was used to precipitate the change shown.

The other five patients in Group I were given wheat, pork, salmon, salmon, and grape juice, respectively, as their specific allergens. Their gastric mucosae presented a uniform change of severe hyperemia, broadening of the rugal folds, boggy edematous appearance, distinct diminution in peristalsis, a lumpy appearance to the mucosa in localized areas, and thick gray mucous adherent in various regions. These changes were most prominent in the lower one-third of the stomach, almost absent in the upper one-third.

The patients comprising Group II presented a uniformly different appearance of mild hyperemia and some increase in the number of highlights with a glistening appearance to the mucosa. No nodulation or edema was present.

The one patient in Group III with asthma not due to food, and the two control cases in Group IV, even though tested in the same manner with salmon, egg, and salmon, respectively, as the specific allergens, failed to show any degree of hyperemia and edema as seen in the patients with the gastric disturbance following the ingestion of a specific allergen. In the control patients the stomach revealed only moderate hyperemia and mild bogginess of the mucosa but in no way comparable to the patients of Group I. None of the minimal changes in the control cases were altered by the injection of adrenalin, 1:1000, subcutaneously.

SUMMARY

1. Definite changes were reproduced in the stomachs of patients who gave a history suggestive of gastrointestinal allergy. Specific antigens were used to elicit the reaction. These changes we consider manifestations of allergic reactions in the stomach, since they were not found in patients devoid of gastrointestinal symptoms.

2. The typical changes characteristic of allergy are as follows: a distinct hyperemia, lumpy or even nodular appearance, edema and thickening of the rugal folds with diminished peristalsis, and grayish mucus clinging to the mucosa. These changes involve mainly the lower one-third of the stomach. Submucosal hemorrhages were seen in one patient.

3. From these observations we believe that it is possible to produce alterations in the stomach mucosa which result in clinical symptoms from the ingestion of a specific allergen.

4. It is suggested that with repeated gastrointestinal allergic insults, the changes in the stomach mucosa may become irreversible and result in permanent damage to mucous membrane.

5. In cases of indigestion where the etiology is not clear, one should consider allergy to specific foods as a possible explanation.

REFERENCES

1. Schittenhelm, A., and Weichardt, W.: Ueber die Rolle der Ueberempfindlichkeit bei der Infektion und Immunität, München. med. Wchnschr. **57**: 1769, 1910.
2. Schittenhelm, A., and Weichardt, W.: Ueber zellulare Anaphylaxie, Deutsche med. Wchnschr. **37**: 867, 1911.
3. Demel, A. C.: La teoria anafilattica dell'ulcera rotonda, Pathologica **15**: 128, 1923.
4. Shapiro, P. F., and Ivy, A. C.: Gastric Ulcer. IV. Experimental Production of Gastric Ulcer by Local Anaphylaxis, Arch. Int. Med. **38**: 236, 1926.
5. Alessio, F.: Contributo sperimentale alla teoria anafilattica dell 'ulcera gastrica, Pathologica **20**: 302, 327, 1928.
6. Vallone, D.: Anafilassi e ulcera gastrica, Arch. ital. di chir. **25**: 535, 1930.
7. Culmone, G. B.: Anafilassi ed ulcera dello stomaco, Policlinico (sez. chir.) **40**: 297, 1933.
8. Guerrisi, A.: Il fenomeno di arthus nello stomaco e nella vescica, Folia med. **20**: 903, 1934.
9. Rössle, R.: Ueber die Merkinale der Entzundung im allergischen Organismus, Verhandl. d. deutsch. path. Gesellsch. **17**: 281, 1914.
10. Knepper, R.: Ueber die Lokalisierung der experimentellen allergischen Hyperergie, Virchows Arch. f. path. Anat. **296**: 364, 1936.
11. Kaiserling, H., and Ochse, W.: Vergleichende Untersuchungen über die allergisch-hyperergische Reaktisn des Mayen-Darmtractus, Virchows Arch. f. path. Anat. **298**: 177, 1937.
12. Afendulis, T. C., and Gulzow, M.: Die allergisch-hyperergische Gastritis. Tierexperimentelle Untersuchungen, Ztschr. f. d. ges. exper. Med. **104**: 167, 1938.
13. Chevallier, R.: L'oedème fugace de la région antropylorique au cours des gastropathies allergigues. Etude gastroscopique, Bronchoscop., oesophagoscop. et gastroscop. pp. 129-136, April, 1935.
14. Paviot, J., and Chevallier, R.: Les gastrophies allergiques, J. de méd. de Lyon **17**: 31, 1936.
15. Moutier, F.: Traite de Gastroscopie. Paris, 1935, Masson & Cie.
16. Lundbaek, K.: Case of Gastroscopically Verified Gastric Edema in Quincke's Disease, Ugesk. f. laeger **101**: 1083, 1939.
17. Wiedemann, H.: Die sogenannten Idiosynkrasien. Ztschr. f. ärztl, Fortbilde. **18**: 630, 657, 1921.

18. Rowe, A. H.: Food Allergy in Differential Diagnosis of Abdominal Symptoms, Am. J. M. Sc. **183**: 529, 1932.
19. Eyermann, C. H.: X-ray Demonstration of Colonic Reaction in Food Allergy, J. Missouri M. A. **24**: 129, 1927.
20. Friedenwald, J., and Feldmann, M.: The Unstable or Irritable Duodenum, J. A. M. A. **103**: 2007, 1934.
21. Gutzeit, K., and Teitge, H.: Die Gastroskopie, Berlin, 1937, Urban & Schwarzenberg.
22. Gerlach, W.: Studien über hyperergische Entzündung, Virchows Arch. f. path. Anat. **247**: 294, 1923.
23. Voss, H., and Voss, F.: Veranderungen der Magensekretion nicht als Ursache, sondern als Folge von Hautkrankheiten, München. med. Wchnschr. **84**: 1486, 1937.

AN APPARATUS FOR DETERMINING THE POLLEN CONTENT OF AIR AND NOTES ON POLLEN SURVEY METHODS

ROLAND C. HAWES, B.S., WILLARD S. SMALL, M.D.,* AND HYMAN MILLER, M.D.
LOS ANGELES, CALIF.

IN STUDYING the relationship of air-borne allergens to clinical symptoms, certain characteristics of the methods used for detecting and measuring air-borne allergens are of more importance than others. These are as follows:

1. Since the clinical data themselves have relatively little quantitative precision, it is of much more importance that the method of air survey be sensitive to low concentrations rather than highly accurate in differentiating various levels of concentration. Errors of even two- or three-fold are of small importance, simply because determination of the degree of a patient's sensitivity is even less precise.

2. The speed with which the method responds to changes in the concentration of an allergen in the air need be but little faster than changes usually seen in patients' symptoms.

3. So far as possible, the method should detect equally readily any of the common allergens. As Durham[1] has pointed out, a method which gives results in terms of number of particles per cubic yard of air falls very far from the ideal because of the cubic relation between particle diameter and weight.

Convenient forms of the mathematical relationships, (A) the Scheppegrell formula as revised by Cocke[2] and (B) the relationship between weight concentration and gravity counts outlined but not formulated by Durham,[1] are as follows:

$$(A)\ n = \frac{2930\ f\ N}{D^2} \qquad (B)\ w = 1.53 \times 10^{-9}\ f'\ D\ N$$

Here n is the number of particles of a particular kind per cubic yard of air; w, the weight of these particles in grams per cubic yard of air; D, particle diameter in microns; N, the number found per square centimeter of twenty-four-hour slide; f and f′, shape corrections to allow for departure from sphericity, surface smoothness, and unity average density. (In general, f will not be equal to f′.)

One point needs emphasis in connection with these formulae. Cocke[3] reported an experimental verification of the revised Scheppegrell formula and discussed an important source of the observed discrepancies

From the Laboratories of George Piness, M.D., and Hyman Miller, M.D.
*Present address, 65 N. Madison Ave., Pasadena, Calif.

between the predicted and observed values of particle concentration; namely, the fact that pollen grains are neither spherical nor smooth. Selection of proper values of their diameters from measurements of the grains is accordingly difficult, yet Cocke failed either to recommend a method for so doing or to report that actually used. In addition he neglected to emphasize the fact that small errors in the diameters become large errors in the calculated concentrations because the diameter appears to the second power in the denominator of the equation. For instance, the difference between the diameter, 18μ which he assumed for ragweed pollen and 20μ assumed by Durham, makes a difference of 23 per cent in the calculated numerical concentration figures and increases his measure of the discrepancy in his results from 32 to 63 per cent.

While it is apparent that methods can vary in the degree to which they satisfy the third condition, actually no method can be made to show an equal sensitivity to all air-borne allergens, since the equality desired is evidently in terms of the ability of the various kinds of particles to produce symptoms rather than in terms of either their weight or number. Thus ten grass pollen grains on a square centimeter of a twenty-four-hour gravity slide may be far more significant in indicating probable trouble for a patient than fifty smut spores, even though the patient is exposed to about the same weight and 125 times the number of particles of the latter (about 3,400 instead of twenty-seven particles inhaled per hour).

On the other hand, the statement that the ragweed count today is 200, whereas it was ten a week ago, has an obvious significance, if the slides were exposed under comparable conditions. As Durham[1] stated, "All agree that the data which may be obtained from uniformly exposed gravity slides by counting the particles caught on a unit slide area are highly satisfactory when dealing with the pollen of a single botanical species—common ragweed, for example."

The ability to produce symptoms is determined much more by chemical and biologic factors than by the physical properties of the allergen particles, whereas it is exclusively the latter which determine the findings with any method which depends on microscopic count of the particles. Furthermore, the chemical and biologic factors are but vaguely understood and certainly not subject to quantitative formulation at present. It is consequently futile and misleading to compare the results between allergens from remotely related species of plants, no matter how the results are obtained or expressed.

Much of the faulty thinking to which counts have led when given in terms of any of the possible absolute measures might readily be avoided simply by recording them in relative terms. Thus, if each worker were arbitrarily to select a particular value for each type of particle counted, say the average count for the 1941 season, as a reference level and to express counts as index values, that is, as percentages of this specified

value, not only would the difficulties discussed be avoided, but attention would be focused on the more immediate problems; namely, the improvement of methods in sensitivity and in freedom from the effects of extraneous factors.

Our own preference would be to express the counts as the logarithms of these percentages in view of the nearly universal proportionality between biologic responses and the logarithms of stimulus quantity (the Weber-Fechner law), a proportionality which has been shown[4] to hold for allergic skin reactions. However, the labor of the additional calculation involved seems hardly justified, at least at present, while the main purpose in so doing can readily be achieved by the use of semilog graph paper in plotting index values for reports. The simple expedient of adding one to each index value places the zero at the bottom of the graph.

THE GRAVITY METHOD

The gravity method of air pollen analysis has some unique advantages from these points of view. It is simple and inexpensive, it comes nearest of any method to giving results proportional to weight concentration,* it has more than adequate speed to follow seasonal changes, and it is subject to improvement in quantitative performance and interpretation. The main sources of error with its use are (1) the much-discussed variations in shape and size of particles, (2) the technique of exposure of the slides, and (3) inevitable statistical variation.

These are important sources of difficulty, yet an examination of their origin and nature may lead to changes in technique and interpretation which minimize them and permit greater confidence in this otherwise highly advantageous method. Such an analysis would appear to be justified both by the immediate practical importance of the problem and by the large total of time and effort spent on it each year by those interested in allergy.

As has been suggested, the variations in shape, size, and density of the particles are of great importance only if it is desired to use the gravity method to obtain precise values of the numerical concentration of particles in the air. In actual fact, the gravity method is not well suited to this purpose and would better be replaced by a technique such as that to be described, or by any of the considerable variety of other precision methods which could be adapted to the purpose.

The technique of slide exposure deserves renewed discussion mainly because one source of difficulty has apparently been overlooked. Under ideal exposure conditions, it is true that, as Scheppegrell[5] said, "The

*To meet this requirement accurately requires an entirely new approach. It seems a fairly simple problem to devise an apparatus which would yield a solution containing the individual soluble allergenic entities (protein, polysaccharide, etc.) from the particles in a given volume of air, and such a method, which would have the desired weight proportionality as well as other valuable features, may be expected to become useful when further progress has been made in the isolation and characterization of these entities and in the development of serviceable methods for their detection and estimation.

number of pollen dropping on a given surface, e.g., a plate, depends only on the number of pollen per unit of air and the velocity of fall of the pollen grains.'' However, one of the assumptions on which this statement was based is that the flow of air over the surface is horizontal and nonturbulent, and departures from this condition will, in general, be reflected by counts which increase with increasing wind velocity, other things being equal. Actually no slide holder has been suggested which fulfills the condition. Data to be presented show that a stiff breeze may cause departures from the values predicted by the Scheppegrell-Cocke formula which are fully as large as those produced by the surface irregularities of pollen grains. It is not unlikely that Barrett's[6] findings of severalfold higher counts on slides exposed in an automobile and on trains than on control slides were principally due to this factor. Furthermore, it renders uncertain the influence of wind on pollen counts as reported by many workers.

There seems little doubt that by attention to this factor in the design of a slide holder the precision of the gravity method could be greatly improved. Tentatively it may be suggested that slides, or perhaps better, cover slips, clamped in an accurately horizontal position and well away from any object tending to interfere with wind flow, as at the top of a mast, would be satisfactory. The whole of the exposed area should of course be coated with adhesive.

Other significant factors include especially the influence of the flora in the neighborhood of the station and that in the direction from which the wind is blowing at any particular time as well as the effect of higher air currents as emphasized by Deamer and McMinn.[7] Each worker will be faced with different problems of this sort, and in fact they vary with each individual patient, so that no general solutions can be found except to note that the common practice of making observations at several stations enables one to estimate the importance of these local factors within the area in which he is interested, once he has some assurance that the differences seen are not due to errors in the method itself.

The third important source of error is that due to statistical sampling variation. While such errors cannot be avoided, their magnitude can be predicted from studies of analogous situations involving the counting of discrete particles, as in making hemocytometer counts and in counting bacteria by plating methods.

In Fig. 1 is shown the relationship between the average count, $\bar{N}$, which would be obtained for a particular uniform air-borne particle if a great many slides were simultaneously exposed under uniform experimental conditions, and the limits* at or outside which 10 or 1 per cent of such parallel counts would be found in each direction (higher or

*The limiting curves were derived from the theoretically applicable Poisson distribution for small values of $\bar{N}$. When $\bar{N}$ is large, this distribution approaches a normal error curve with standard deviation squared equal to mean, which was used to fix the position of the curves at the right-hand edge of the graph.

lower than $\bar{N}$). The vertical axis of the plot gives the ratio between each individual count and the average value. Ratios can fall only at the points of intersection of the system of slanted straight lines which outline the limit curves with a vertical line through the particular value of $\bar{N}$.

It may be seen that even under ideal conditions of slide exposure quite large counts must be obtained to limit the error expected to a small percentage. The fact that the average count must be 2.3 or over before one or more particles are found on 90 per cent, and 4.5 or over before some are found on 99 per cent of parallel counts, deserves especial attention.

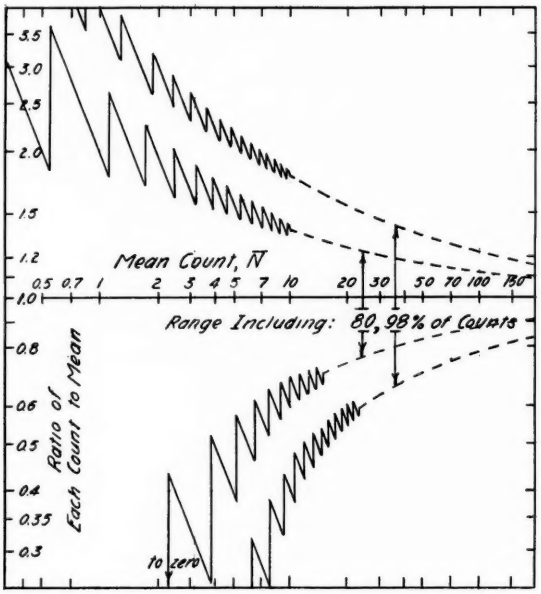


Fig. 1.—Plot of error limits in pollen counting (see text).

ALTERNATIVE METHODS

In order to study the quantitative reliability of the gravity method and to supply correction factors for the Scheppegrell-Cocke formula, it is necessary to have recourse to other methods. Many have been described, but the only one which is capable of giving direct, reliable counts of the number of particles in a given air volume is that of Cocke.[3] It has, however, the practical disadvantage that a very large slide area must be examined for each run.

Feinberg and Steinberg[8] attempted to estimate the reliability of the gravity slide method by collecting a sample of air of known volume and permitting its content of pollen to settle completely onto slides at the bottom of the sample container. While at first glance this might seem an admirable method, it is subject to several difficulties, some of which

apparently affected their experiments, since measurements served to verify the original Scheppegrell formula and were therefore in error to the same extent as the formula, i.e., about 400 per cent.

Various other workers have suggested placing slides in a stream of air from a fan or blower,[9, 10] facing slides toward the wind by means of a weather-vane[11-13] or rotating them in a special holder,[14] also placing them in the current of a moving vehicle.[7, 15-18] These expedients have in common the fault that they do not give data which are subject to simple, direct interpretation. Where they were used for quantitative work they were calibrated by reference to gravity slide readings, and their absolute accuracy could therefore not exceed that of the latter method.

EXPERIMENTAL METHOD

Apparatus.—We attempted several years ago to develop an absolute method which would be as free from errors as possible while retaining practical utility. With the generous cooperation of the Western Precipitation Company of Los Angeles, who have been pioneers in the field of dust collection and analysis, we investigated the commonly used methods, including electrostatic, centrifugal,[19] filtration, and impingement.[20, 21] Practical considerations, including cost, interpretability of results, portability, and especially the desirability of having only a small area to examine under the microscope, eliminated all but the impingement method.

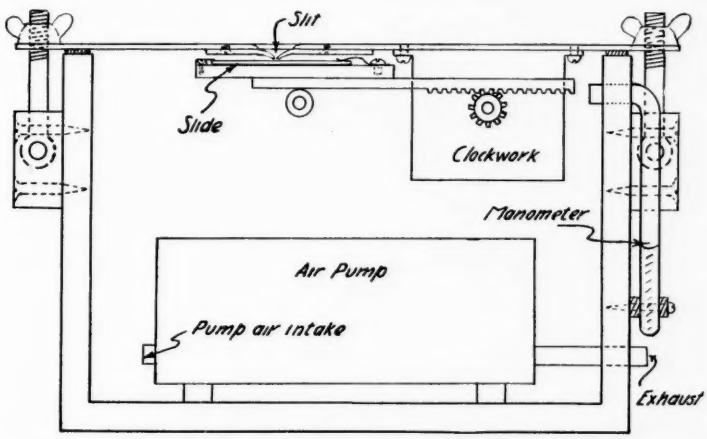


Fig. 2.—Simplified cutaway view of apparatus for determination of air-borne particles.

The apparatus appears in Fig. 2, which shows it as it would look if one side of the box were cut away.

Air is drawn into the partially evacuated box through a fine slit, 0.20 mm. wide by 10 mm. long, in the rubber-gasketed cover plate at a rate of about 0.1 cubic foot per minute. The average velocity of the air in the slit is about 2,400 cm. per second, or 53 miles per hour. This

thin, high velocity air stream strikes an adhesive-coated slide about 2 mm. away from the orifice, depositing its load of dust over a surface less than three times as wide as the slit. The slide is moved lengthwise at a rate of 2.5 mm. per hour by an electric clock mechanism attached to the cover plate. A twenty-four-hour run occupies about three-fourths of the length of a standard three-inch slide.

The air, freed from its content of pollen as well as of most of its other dust constituents, travels to the inlet of an air pump of the type used to aerate small fish ponds* and is exhausted from the pump through a silencer (not shown) to the outside through a tube sealed into the box wall. A water manometer mounted on the outside wall serves to measure the vacuum within the box.

The rate of air flow through the slit was measured with an inclined-tube draft gauge by connecting it to an inverted rubber cup sealed over the slit. Measurements at the air outlet served to detect leaks around the gasket.

The manometer on the side of the box was useful in showing whether the pump was operating properly and the gasket sealed air tight, and in giving warning in case the slit became badly clogged during a run.

The slit was cleaned at the start of each run by passing narrow strips of absorbent paper through it before and after wetting it with acetone. It seldom clogged so badly as to require recleaning during a run.

Sources of Error.—The principal sources of error with this apparatus are the following:

1. There may be inaccuracies in the measurement of flow rate. The draft gauge could be read to better than 5 per cent, and the pump was found to give constant flow over the range of pressure encountered in operation, within 5 per cent. Nevertheless, large particles which obstruct a part of the slit do cause decreases in the amount of pollen caught both because they decrease the total flow rate (but increase the vacuum, and so increase the flow rate through the unobstructed parts of the slit as well as through any leaks which may be present) and because they and any irregularities on the slit walls tend to "filter" pollen out of the air.

As will be seen in connection with the discussion of experimental results, these effects together may cause decreases in average counts of about 25 per cent at the end of a twenty-four-hour run. The contribution of each source of error is indicated by the fact that flow rates in these experiments were found to decrease by about 12 per cent on the average during twenty-four hours, and by the results of attempts to determine the number of pollen grains detained at the slit, washing it with acetone, catching the wash on slides and counting the pollen obtained. The latter might at times amount to as much as 10 per cent of that on

*Haddaway Mfg. Co., Los Angeles

the corresponding machine slides. Both errors have been diminished in later work by improving the gasket construction and by using a highly polished slit.

2. The pollen grains may fail to strike or to adhere to slides. All slides were coated with glycerin jelly. Some were exposed by placing them on the pump housing inside the case; also the bands of jelly on each side of the dust track were often examined for pollen which had not been removed from the air stream. Only rarely was even a single pollen grain seen. Comparisons with ordinary gravity slides indicated that the efficiency of removal was always better than 95 per cent for all pollen types.

3. Dust may fall by gravity onto the cover plate and be blown into the slit. We tried to minimize this "wind error" by cementing a narrow collar about one-sixteenth of an inch thick around the slit opening, also by keeping the cover clean and sticky by wiping with an oiled rag. We have no way of determining the magnitude of this error, but work described in connection with Table I indicates that the gravity method was subject to larger errors caused by the wind than was the machine under our experimental conditions. It should be pointed out that the gravity method as it is ordinarily performed is subject to this same error as well as to the effect of turbulent air-flow mentioned previously.

4. A real difficulty in examining slides exposed with the apparatus is due to the fact that it is highly efficient in the collection of fine dust and smoke particles. Pollen grains are relatively more difficult to find and identify than on gravity slides. The stain content of the jelly adhesive is an almost indispensable aid for this purpose, since few of the dust particles absorb stain with the result that pollen is conspicuous against the background of grey, brown, or black debris. Unfortunately, no such advantage is gained for fungus spores.

5. Electrostatic forces may cause errors. We do not know of directly pertinent data which would permit us to estimate their importance. It seems probable that if they are significant they would be less so with the apparatus than in the gravity method because of the short time they would be able to act in the rapidly moving air stream.

Findings With the Apparatus.—Twenty-six runs of twenty to twenty-six hours' length were made with the first model of the apparatus between Dec. 28, 1938, and Jan. 31, 1939. This is the only extended series of runs for which the counts were made by covering the entire area traversed by the slit, and therefore the only one for which counts could be satisfactorily interpreted in terms of the air flow. Unfortunately it was done at a time when the pollen content of the air in Southern California is at its lowest; nevertheless, sufficiently large total counts were obtained to make the figures and calculations of some significance.

Gravity slides were exposed beside the slit of the machine. Both slide and slit were protected from rain by a shelter similar to that described by Acquarone and Gay.[22]

The station was a platform two feet above the laboratory roof. The building is a flat-roofed two-story structure in a business district about a mile west of the center of Los Angeles. Residential and business areas surround it for miles in all directions. Westlake Park, an area of four city blocks, about half of which is lake, lies one block to the west and northwest, in the direction of the prevailing winds.

Complete weather data, including hourly wind direction and velocity, were obtained through the cooperation of the United States Weather Bureau station in downtown Los Angeles.

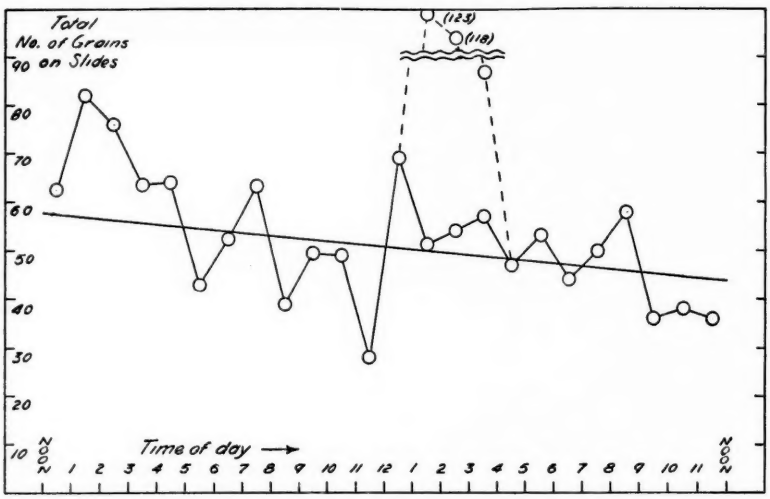


Fig. 3.—Plot of total hourly pollen counts for twenty-six runs with the apparatus. The least-squares straight line was calculated for the points between 3 P.M. and 11 A.M.

Counts were made by one person (W. S.). They were tabulated by the hour of the day for the machine slides. All runs were started near noon, at an average time of 12:42 P.M. The results are plotted in Fig. 3. There were a few runs for which the data were incomplete over periods of up to five hours due to apparatus breakdown or failure to change the slide within twenty-six hours of the start of the run. They amounted altogether to 2.1 per cent of the total time. Since the gravity slides were exposed during these times that the machine was inoperative, the machine counts were corrected by assuming that the average hourly count for the run would have been obtained.

At 1:00 A.M., January 28, the wind suddenly doubled in velocity and veered from southwest to northwest. The maximum velocity reached was 22 miles an hour. (Average for the series was 6.1 miles an hour.) Coincident with this change there was a shower of palm pollen for four

hours which brought the day's palm pollen count from about 10 to 178 (machine). The day before and after showed 7 and 12 grains, respectively. The gravity slide count was also much increased for that day. This phenomenon was attributed to the palm trees at the north edge of Westlake Park, and the curve for this time of day is shown double, the lower curve being corrected as though the apparatus had been out of operation for this period.

Examination of the chart shows that the general trend of the counts is downward from the start of the runs. A least-squares straight line was drawn through the points between 3 P.M. and 11 A.M., the hours of latest start and earliest conclusion of any run. It slopes downward by 0.58 gr. per hour or 14 gr. per day or, taking its intersection with the average starting time as a base, by 1 per cent per hour. It was assumed that this decrease was due to the sources of error described; namely, to decrease in air flow and to the "filtration" effect of the slit. Another short series of runs gave similar figures.

TABLE I

COMPARISON OF GRAVITY AND MACHINE COUNTS

KIND OF POLLEN	"AVERAGE" DIAMETER (μ)	NUMBER* ON GRAVITY SLIDES	NUMBER ON MACHINE SLIDES		DISCREPANCY IN PER CENT OF PREDICTED
			PREDICTED FROM GRAVITY	ACTUAL (CORRECTED)	
Palm†	20	28	303	268	−12
		44	476	199	−58
Eucalyptus	20	24	260	105	−59
Alder	22	50	447	293	−34
Artemesia	24	50	376	319	−15
Grass	33	9	36	25	−31
Cedar	30	42	202	224	+11

*Total for twenty-six days; 3.6 sq. cm. examined each day.

†Palm counts: First line, twenty-five days, omitting windy day described in text; second line, count for windy day alone.

If the data are corrected for this downward trend, it is seen that there was no consistent diurnal fluctuation of pollen counts, at least for the particular station, season and year examined. If, as theory predicts, the hourly counts are distributed according to the Poisson law, their standard deviation should be equal to the square root of their mean value. As a rough check, the average deviation was found to be within 3 per cent of the square root of the mean. The points just before and after midnight are perhaps lower and higher than would have been expected, and the original data showed this to be a rather consistent finding; but since no other explanation suggested itself, it was thought probably to be due to a fault in the scale which was cemented to the microscope mechanical stage to facilitate division of the counts by hours. Individual days showed apparently significant fluctuations, in agreement with previous observations.[11, 23]

The only other discernible effect of weather on the counts occurred during a rainstorm. Within two hours of the start of precipitation the counts fell almost to zero (2 a day, instead of about 60), and remained low for a day after the rain stopped, then rapidly rose to the prerain level. Gravity counts fell proportionately.

We have used the data from this series of counts to check the Scheppegrell-Cocke formula. The results are shown in Table I. Palm counts are given twice, once for the windy day mentioned above, the other for the remainder of the series. All the more commonly encountered types of grains are included in the table.

The correction for the times when gravity slides were exposed while the machine was not operating, and another for the effect of slit clogging (increasing all counts by 12 per cent), were applied to the machine results.

The effective grain diameters chosen for the purpose of calculation are the averages of measurements of the longest and shortest diameters of a number of dry grains of each type of pollen.

It may be seen that in general the results confirm the correctness of the gravity formula. Considering the important influence of possible errors in the values taken for the effective diameters in the calculations, the agreement seems remarkably good.

The check of the Scheppegrell-Cocke formula was repeated with data from four runs made on Nov. 28 and Dec. 2, 4, and 5, 1941, using the newer model of the apparatus. Because it was done at the same season of the year, the pollens seen in larger amounts were of the same species as before. Machine counts were not corrected for the decrease during these runs, as they had been before, because insufficient runs were made to determine the magnitude of the correction factor. As stated before, checks of flow rate, which averaged 0.088 cubic feet per minute, and of "filter error" by counting slit washings, suggested that the correction needed with the newer apparatus was smaller than 12 per cent.

Discrepancies, calculated as before, between gravity and uncorrected machine counts were as follows: palm pollen, –38 per cent; eucalyptus, –59 per cent; grass, –53 per cent; cedar, –3 per cent; smut (assumed diameter, 6μ), –35 per cent. Total machine slide counts were about one-fourth as large as in the earlier series of runs, while a sufficiently large area (about 15 sq. cm.) of the two gravity slides exposed with each run was counted to make the gravity totals as large as before. Smut, which was counted for but one day, gave totals of 264 on the machine slide and 15 on 14 sq. cm. of gravity slide.

These discrepancy figures are not significantly different from those given in Table I.

It is noteworthy that the figures predicted from gravity slide counts average somewhat higher than the machine counts. Since the effect of

pollen falling on the lid and being blown into the slit would be in the opposite direction, we are inclined to attribute the discrepancy to error in the gravity counts caused by the turbulent flow of wind over the slides. The palm pollen counts given separately for the windy day described tend to confirm this conclusion, since the discrepancy was greater on that day than for the average of the other days.

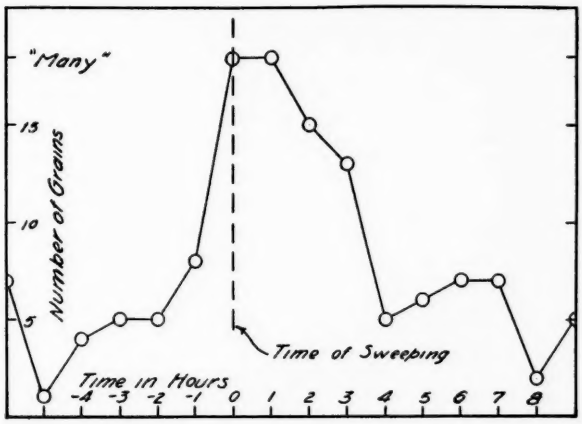


Fig. 4.—Composite graph of hourly pollen counts in relation to time of sweeping, for seven runs made indoors. (During and immediately after sweeping, accurate counts could not be made because of debris on slides.)

A few runs were made with the apparatus during July and August, 1939, in the home of one of us (W. S.) with the thought that some observation might be made to account for the frequency with which asthmatic attacks occur in the early morning hours. This hope was not realized, but another finding of considerable interest was noted. The time at which the room had been swept could easily be seen, macroscopically by the heavy dark deposit of dust, and microscopically by the sudden burst of small hairs and fibers of various kinds, fine particles of unidentifiable material of a great variety of shapes and sizes, mold spores, and of a greatly increased number of pollen grains, a considerable proportion of which were types not commonly seen on gravity slides. These materials slowly decreased in concentration in the air during a few hours after the sweeping was completed. In Fig. 4 is shown a composite curve of the pollen counts in relation to the time of day at which the room was cleaned. Exact counts during the cleaning and for an hour afterward could not be made in some instances because grains were usually partly or completely covered with debris.

This observation, in addition to emphasizing the hazards of sweeping, suggests that one of the difficultly identifiable allergenic factors in house dust may be pollen from cut flowers. While as a rule these are not wind pollinated, as they mature and dry in a vase they often shed considerable quantities of pollen which may easily lose its adherent quality through drying, oxidation, or coating with fine dust particles. It seemed sig-

nificant that the pollen counts during and after sweeping were, as well as they could be estimated, of the same order of magnitude as are commonly seen here on slides exposed out of doors during the peak of the pollen season.

SUMMARY

1. An apparatus is described which is adapted to direct determination of the number of pollen grains or other particles in known volumes of air, with which abrupt changes in counts can be easily followed.

2. It is confirmed that the Scheppegrell-Cocke formula for calculating air pollen concentration from the results of gravity slide experiments is approximately correct. The main sources of error are the effect of wind on the counts and the determination of the effective diameter of the particles.

3. No consistent diurnal changes in pollen counts could be detected under the conditions of the experiments.

4. Rain quickly and completely freed the air from pollen, but other short-time effects of weather were negligible except for a shower of palm pollen during a sudden shift of wind, which was attributed to a nearby group of trees.

5. A series of runs made indoors showed vividly the effect of ordinary house cleaning methods on the dust content of the air, and especially on its pollen content. The possible significance of pollen from cut flowers is discussed in this connection.

6. A review of the problems involved in air pollen assay shows that the gravity method has several unique advantages over other methods which are practicable at present, while it has no serious disadvantage if pains are taken to avoid the common faults in the design and arrangement of the exposure station.

7. It is suggested that pollen counts be reported as index figures, that is, as percentages of specified, arbitrarily adopted, standard counts for each type of pollen, in order to avoid the erroneous implications inherent in previously employed counting scales.

We are indebted to O. C. Durham, Chief Botanist, Abbott Laboratories, for encouragement and helpful criticism of the manuscript.

REFERENCES

1. Durham, O. C.: J. ALLERGY **13**: 31, 1941.
2. Cocke, E. C.: J. ALLERGY **8**: 601, 1937.
3. Cocke, E. C.: J. ALLERGY **9**: 458, 1938.
4. Miller, H., Hawes, R. C., and Piness, G.: J. ALLERGY **12**: 335, 1941.
5. Scheppegrell, W.: Arch. Int. Med. **19**: 959, 1917.
6. Barrett, C. E.: J. ALLERGY **5**: 406, 1934.
7. Deamer, W. C., and McMinn, H. E.: J. ALLERGY **6**: 480, 1935.
8. Feinberg, S. M., and Steinberg, M. J.: J. ALLERGY **5**: 19, 1933.
9. Vaughan, W. T., and Cooley, L. E.: J. ALLERGY **5**: 37, 1933.
10. Duke, W. W.: J. ALLERGY **2**: 471, 1931; J. A. M. A. **99**: 1686, 1932.
11. Wilmer, H. B., and Cobe, H. M.: J. ALLERGY **3**: 63, 1931.

12. Penfound, W. T., and Efron, B. G.: Proc. Soc. Exper. Biol. & Med. **27**: 650, 1929.
13. LaRush, F.: J. ALLERGY **5**: 306, 1933.
14. Durham, O. C.: Aerologist **11**: 10, 1935.
15. MacQuiddy, E. L.: J. ALLERGY **6**: 123, 1935.
16. Scheppegrell, W.: M. J. & Rec. **119**: 185, 1924.
17. Stakman, E. S., Henry, A. W., Curran, C., and Christopher, W. N.: J. Agr. Research **24**: 599, 1923.
18. Meier, F. C., and Lindberg, C. A.: Scient. Monthly **40**: 5, 1935.
19. Wells, W. F.: Am. J. Pub. Health **23**: 58, 1933.
20. Drinker, P., and Hazard, W. G.: U. S. Patents Numbers 2,076,553 and 2,076,554.
21. Robertson, A. C., Mulder, J. G., and VanSaun, F. G.: Indust. & Eng. Chem. (Analyt. ed.) **13**: 331, 1941.
22. Acquarone, P., and Gay, L. N.: J. ALLERGY **2**: 336, 1931.
23. Durham, O. C.: J. ALLERGY **1**: 12, 1929.

A VEGETABLE MILK SUBSTITUTE: TARO

BENJAMIN F. FEINGOLD, M.D.
LOS ANGELES, CALIF.

WITH the more widespread recognition of the role of allergy in the management of diets of infants and children, and with the appreciation that milk is a very common offender, the need for satisfactory milk substitutes is being felt more keenly by clinicians. The importance of milk as a source of readily available calcium makes its omission a difficult gap to fill. This is particularly true in the diets of infants and children, at an age period when an adequate calcium intake is essential for normal growth and development. Any substitute for milk must not only offer essential substances, as protein, carbohydrate, fat, and mineral salts, but it must be in a form readily adapted to infant feeding. In addition, the food should be palatable.

Many vegetable substitutes for milk have been recommended, such as almond, cocoanut, soybean, and poppy seed milk. Of these products, the recipes derived from soybean flour have been the most popular. In some cases of milk sensitivity, there may be an associated soybean intolerance also. Even in the absence of a demonstrable sensitivity to soybean, young infants frequently do not tolerate the product very well.

TARO

Taro (*Colocasia esulenta*)[1] is one of the oldest economically important food crops known to man, and word of its excellence as a food has been handed down throughout the ages. It was mentioned in Chinese literature as early as 100 B.C. and has been grown in Egypt since before the time of Pliny (23-79 A.D.) who makes mention of it as one of the established food plants of the country. Its highest cultural level has been attained in the Hawaiian Islands, and for over 1500 years it has provided the basic food of the natives of these Islands.

In most parts of the world the taro is cooked and eaten in much the same manner as the potato or the sweet potato, but in Hawaii it is commonly eaten in the form of a mush, known as "poi." Miller[2] states that unlike most people of fine stature, the Hawaiian race had no grains and no milk, yet it compares most favorably with other races in both stature and physical development. The physical excellence of Hawaiians

From the Allergy Service of Dr. George Piness, Los Angeles Children's Hospital.

and other Polynesians has long been considered to be intimately associated with their diet, and a great deal of scientific research has been devoted to a study of this basic food.

The establishment of the Ewa Health Project in 1930 marks the beginnings of an extensive and well-organized body of research which has continued uninterrupted to the present day. As a result of the important findings of the Ewa Project, the United States Department of Agriculture, in cooperation with the University of Hawaii, instituted a further research project in 1935[1] which has dealt not only with the nutritional aspects of taro, but also with the equally important problem of extending its use through the development of stable and marketable products. As a result of these investigations, a dehydrated taro meal has been made available which retains in very large measure the natural attributes of the freshly cooked taro root.

Taro is primarily a carbohydrate food as is disclosed by the analyses of steamed taro and of taro meal (Table I).

TABLE I

ANALYSIS OF STEAMED TARO[3]

CONSTITUENT	PER CENT
Water	64.0
Protein	1.18
Ether extract	0.17
Starch (acid hydrolysis)	29.31
Sucrose	1.40
Reducing sugars	0.39
Ash	0.59
Calcium	0.026
Phosphorus	0.061
ANALYSIS OF TARO MEAL[4]	
Moisture 70 to 75° C. vacuum	7.75
Ash	1.55
Protein	2.00
Ether extract	0.56
Crude fiber	1.42
Starch	77.91
Reducing sugars	0.52
Sucrose	0.11
Pentosans	2.58
Dextrin	0.52
Total	94.92
Ash	1.55
Calcium	0.089
Chlorine	0.0693
Copper	0.0003
Iron	0.0043
Magnesium	0.082
Manganese	0.0010
Phosphorus	0.149
Potassium	0.408
Sodium	0.000
Sulphur	0.0147
Zinc	0.00010
Acid-base balance (cubic centimeters of normal acid to neutralize 100 Gm.)	19.07

According to Miller,[2] steamed taro is rich in vitamin B (B complex) and contains appreciable amounts of vitamin A but is a poor source of vitamin C. Potgieter[3] states that taro contains (on the dry basis) about three-fourths as much vitamin B_1 as whole wheat flour and is a good source of vitamin G. Taro flour is reported to contain approximately 0.9 I.U. per gram of vitamin B_1.

The following recipe based on taro meal is offered as an addition to the small group of vegetable milk substitutes already available. At the current market prices a quart of the formula can be produced for about eleven to thirteen cents. The low cost and the facility of preparation makes available an additional product which should, to some degree, help ease the problem of management in milk-sensitive children.

RECIPE

Ingredients:

(1) Pvo meal (taro)	20.0 Gm.	(5⅓ teaspoonfuls)
(2) Clear gelatin	4.0 Gm.	(1⅓ teaspoonfuls)
(3) Vegetable oil (olive, cottonseed, corn, sesame)	10.8 Gm.	(3 teaspoonfuls)
(4) Corn syrup	7.5 Gm.	(½ tablespoonful)
(5) Calcium gluconate	2.0 Gm.	(2 teaspoonfuls)
(6) Sodium chloride	2.4 Gm.	(½ teaspoonful)
(7) Water to make	240 c.c., or 8 ounces	

Preparation:

Weigh and mix the dry materials. Add the oil and mix to a paste. Add the corn syrup and water to make 240 c.c., or 8 ounces. Cook over the direct flame for three minutes, stirring while cooking. Cool the mixture and restore to the original volume by the addition of water.

TABLE II

COMPARATIVE MG. PER CENT IN 240 C.C.

	PROTEIN	FAT	CHO	P	Ca
Human milk*	3.0	9.6	16.8	0.037	0.0792
Cow's milk*	8.4	9.6	10.8	0.256	0.288
Taro formula	4.4	10.81	22.8	0.03	0.196

*Based on Composition of Milk cited by Brennemann.[4]

TABLE III

CALORIC VALUE OF 240 C.C. OF RECIPE

20.0 Gm. Poyo meal	70.6 Calories
4.0 Gm. Gelatin	16.0 Calories
10.8 Gm. Oil	97.2 Calories
7.5 Gm. Corn syrup	30.0 Calories
Total	213.8 Calories
Caloric value per ounce	26.67 Calories

DISCUSSION

It will be noted that both the fat and protein contents of taro (Poyo meal) are low. The fat percentage can be corrected easily by the addition of almost any vegetable oil. The choice of oil should be governed by the tolerance of the patient and the cost of the product. In our ex-

perience olive oil makes the most palatable mixture. However, for economic reasons and also because of specific sensitivities, we have on occasion substituted other oils such as cottonseed oil or corn oil with equal success.

Augmenting the protein content of the formula to a percentage comparable to that of milk has been more difficult. A protein substance that can provide all the amino acids essential to growth and also mix readily in a formula as suggested could not be found. Although gelatin is lacking in two essential amino acids, tyrosine and tryptophane, it was considered the most satisfactory. Gelatin is a readily available source of low cost protein. In the recipe recommended, it not only mixes readily with the other ingredients without detracting from the palatability of the formula, but it also actually helps to hold the other ingredients in a uniform suspension. When cool, the mixture forms a light gel but when warmed it liquefies and readily passes through a nipple. Since the available protein is incomplete, the formula cannot be used as the sole source of food for prolonged periods. For brief intervals in infant feeding, such as in determining the tolerance for milk by elimination, it can be recommended. In older infants and children, who receive foods other than milk which provide a source of protein, this formula may be considered a complete substitute for milk.

The carbohydrate of taro is for the most part in the form of starch (77.9 per cent) which is readily available to the body.[5] Additional carbohydrate in the form of corn syrup, which mixes readily, is advisable not only to increase the caloric value of the mixture, but also to add to the taste. In cases where corn syrup is not well tolerated, any carbohydrate may be used.

TABLE IV

SOURCE OF CALCIUM	UTILIZATION (AVERAGE)
Milk[1]	78.0%
½ Milk	40.0%
½ Spinach[7]	
½ Milk	71.5%
½ Kale[6]	
Taro[3b]	82.0%

The calcium of taro is exceedingly well utilized,[3, 6] comparing favorably with milk calcium in this respect. Table IV compares the source of calcium from taro and other common foods.

On the basis of 0.089 per cent of calcium in taro meal, the 20.0 Gm. of taro meal in the suggested formula would supply 0.0178 Gm. of calcium. By the addition of 2 Gm., or 2 teaspoonfuls of calcium gluconate, the available calcium is increased by 0.1786 Gm., making the total available calcium in 240 c.c. of the formula, 0.1964 Gm. The available calcium in an equal volume of cow's milk on the basis of 120 mg.[7] of calcium for each 100 c.c. of cow's milk is 0.288 Gm. However, in

formula writing for infant feeding, cow's milk is usually diluted by approximately one-third, so that the average cow's milk formula of a corresponding volume would provide approximately 0.19008 Gm. of calcium, which is practically the same as that provided in the taro meal formula. The value of calcium provided by cow's milk, rather than the value contained in breast milk, has been taken as a guide for calculating the calcium content of the formula. This is in order to insure the absorption of an amount corresponding to the low average calcium absorption of breast-fed infants. As has been pointed out by many nutritionists, the calcium of human milk is more readily absorbed than the calcium of either cow's milk or vegetables.

The chlorine content of taro is 0.0693, which compares favorably with that of cow's milk (0.76), and is considerably higher than the percentage for human milk (0.038). There is no sodium chloride in either human or cow's milk. Since taro contains no sodium, the addition of sodium chloride is considered advisable both as a source of the sodium ion and to improve the taste of the formula.

In Table I it will be noted that taro is also an entirely satisfactory source of other minerals such as iron, copper, manganese, and iodine. It will be observed that the iron content is 0.0043 per cent, which is considerably higher than that for either human or cow's milk. There is, however, no information on the availability of the iron content to the body.

It has been pointed out that taro is primarily a carbohydrate food. When sensitivity to cereals or other starchy foods is encountered in either infants or older children, taro provides an excellent substitute. It should be kept in mind, however, that sensitivity to taro does occur. In the Allergy Clinic of the Los Angeles Children's Hospital positive skin reactions to taro have been observed, but they occur far less frequently than the positive reaction for either milk or the grains.

SUMMARY

1. A low-cost recipe based on taro (Poyo meal) is offered as a milk substitute for use in the diets of milk-sensitive children.

2. The recipe is easy to prepare, is palatable, and may be offered from a bottle.

3. Taro may also be used to advantage as a substitute for the starchy foods.

REFERENCES

1. Payne, J. H., Ley, G. J., and Akau, G.: Processing and Chemical Investigations of Taro, Bulletin 86, Hawaii Agricultural Experiment Station of the University of Hawaii, June, 1941.
2. Miller, C. D.: Food Values of Poi, Taro, and Limu, Bulletin 37, Bernice P. Bishop Museum, Honolulu, 1927.

3. Potgieter, M.: (a) Taro (Colacasia esculenta) as a Food, J. Am. Dietet. A. **16:** 536, 1940.
(b) The Utilization of the Calcium and Phosphorus of Taro by Young Rats, J. Am. Dietet. A. **16:** 670, 1940.
(c) The Utilization of the Calcium and Phosphorus of Taro by Young Women, J. Am. Dietet. A. **16:** 898, 1940.
4. Brenneman, Joseph (Editor): Practice of Pediatrics, Hagerstown, Md., 1933, W. F. Prior Co., Inc., vol. 1, chap. 26, p. 3.
5. Langworthy, C. P., and Deuel, H. J., Jr.: Digestibility of Raw Rice, Arrowroot, Canna, Cassava, Taro, Tree-Fern and Potato Starches, J. Biol. Chem. **52:** 251, 1922.
6. Fincke, M. L., and Sherman, H. C.: The Availability of Calcium From Some Typical Foods, J. Biol. Chem. **110:** 421, 1935.
7. Best and Taylor: Physiological Basis of Medical Practice, Baltimore, 1937, William Wood & Co., p. 1051.

6222 WILSHIRE BOULEVARD

Special Article

ALLERGY IN GERMANY*

WALTER LANDAU, M.D., AND LESLIE N. GAY,† M.D.
BALTIMORE, MD.

THIS book is the first comprehensive German publication on allergy since the appearance of Kämmerer's work in 1934, and although it cannot be assumed that all its viewpoints are generally accepted by German allergists, it gives a good insight in the present state of opinions on this subject in Middle Europe. The work is called a textbook, but it is rather a series of monographs, its twenty-two sections being the contribution of eight different authors. The volume no doubt owes its peculiar note to the scientific background of its editors. Berger was a pupil of Doerr in Basel, one of the founders of experimental anaphylaxis, whereas Hansen worked in Heidelberg with von Krehl, who was one of the outstanding men of German internal medicine of the past.

The editors point out in their preface that science of allergy inaugurates a fundamental turn and a decisive progress in many sections of medicine; they feel that this development still going on renders it necessary to present, beside the facts, the many problems encountered in this field. Thus, much space has been devoted to the discussion of experimental work and problematic points. In their endeavor unfortunately the authors did not escape a certain tendency of oversystemizing. In an attempt to cover even the most remote possibility of thinkable events and to bring them in a prearranged scheme, they sometimes lose themselves in pure speculation and make parts of the book not easy reading. On the other side, such a method, of course, may be productive in finding unexpected relations and in encouraging new trends of ideas. It follows from the general viewpoint of the editors that the book could not be restricted to allergic diseases; its purpose was to seek an understanding of allergic phenomena everywhere and to assign them their place in general medicine. Therefore, such phenomena occurring in the gastrointestinal tract, in the eyes, in the joints, and in the circulatory system are broadly discussed with equal rights beside asthma, hay fever, urticaria, and eczema. As to the discussion of clinical facts there was no intention to give a complete survey of all

*A review of *Allergie Ein Lehrbuch in Vorlesungen* by K. H. Baagoe, Kolding; W. Berger, Graz; E. Hanhart, Zürich; K. Hansen, Lübeck; F. Klinge, Münster; W. Riehm, Giessen; H. Schmidt, Marburg; K. Schreiner, Graz. Edited by W. Berger and K. Hansen, Leipzig, 1940, Georg Thieme, 728 pages.

†From the Protein Clinic of the Medicine Dispensary of the Johns Hopkins Hospital.

known data and experiences but rather to present significant examples for the various phenomena. Thus, the volume contains many interesting details, but it would not be satisfactory as a reference book compared with American standard textbooks.

A discussion of allergy, however, cannot even be limited to allergy itself, as Berger points out in the first introductory section, for we have to deal with certain conditions which may be brought on by an allergic mechanism but may have other causes as well. The author groups these conditions together in the following list which gives the syndromes and diseases in the various body systems:

I. 1. Laryngospasm
2. Vasomotor rhinitis
Sinusitis
Glottis edema
Pharyngolaryngitis
Tracheobronchitis
Bronchial asthma
Pulmonary edema

II. 1. Circulatory shock, universal local
Fall in blood pressure
Angiospasm
Paroxysmal tachycardia and arrhythmia
2. Inflammation, universal local

III. 1. Colics
Dyskinesias
Disturbance of secretion
2. Acute gastritis and enteritis
Membranous colitis
Chronic gastritis and enteritis

IV. 1. Pallor
Hyperemia
Itching
Pruritus
2. Erythema
Eczematous dermatitis
Urticaria
Angioneurotic edema
Purpura
Arthus phenomenon

V. Epilepsy
Migraine
Ménière's syndrome

VI. Phlyctenulas
Conjunctivitis

VII. Humoral and cellular eosinophilia

VIII. Fever
Drop in temperature
Disturbance in metabolism

IX. 1. Arthralgia
2. Arthritis

X. Rare and questionable types

XI. Infection phenomena
Rheumatism phenomena

A second group, listed as "the more rare, questionable, and not generally recognized types" comprises the following:

Conjunctivitis vernalis
Polypous rhinitis
Fibrinous bronchitis
Bronchotetany
Glossitis, stomatitis
Angiospastic dysbasia
Angina pectoris
Raynaud types
Cerebral angiospasm and hemorrhages
Thromboangiitis obliterans
Endocarditis
Pylorospasm, cyclic vomiting
Dyskenesia of biliary tract and urinary tract
Salvarsan jaundice, serous hepatitis
Exudative diathesis
Psoriasis
Iritis, keratitis
Lymph node swelling
Endocrine disturbances
Erythema multiforme
Allergic factors in gout

Associated with these conditions is a definite group of causes; namely, the nonallergic causes consisting of physical, chemical, hormonal, and psychogenic reflex causes, and the allergic causes divided in nonanimated exo-allergens, body allergens, and parasitic allergens. Any of these causes may produce any of the mentioned conditions. The characteristic

feature in such conditions is a common inherited or acquired constitition of certain tissues, particularly of the peripheral blood vessels, connective tissues, and the nerve end apparatus. This common constitution consists in a definite susceptibility for selected and preferred stimuli and in the tendency to typical ways of tissue response. The author states quite correctly that the name allergic diseases, therefore, is not satisfactory and that a different name should be found. In the meantime he talks of "facultative allergy-determined conditions," using the term facultative as it is common in bacteriology in the compound facultative anaerobic bacteria.

The term allergy itself is to be understood to comprise all constitutions and events that are based on the existence and the intervention of antibodies and equivalent substances which includes serum reactions, immunities, and allergic diseases. The term idiosyncrasy is used for sensitization by previous natural contact with allergens, the term anaphylaxis for sensitization through experimental or therapeutic introduction of proteins or haptens. But in accord with Doerr in Europe and with Zinsser in this country, no basic difference is acknowledged between idiosyncrasy and anaphylaxis; both are parts of allergy.

There is a certain number of unspecific phenomena accompanying sensitization or anaphylaxis; e.g., the par-allergy of Moro, meaning the altered reactivity of an allergic organism toward unspecific stimuli. Those phenomena have been embraced with the term "umstimmung" or alteration and are thought to be due perhaps to a reactive body still unknown. This problem is discussed in the section on Experimental Foundations of Allergy (Schmidt) which also deals with the possible existence of two different antibodies in allergic reactions, for it has been found that a discrepancy exists between the serum of children suffering from eczema due to egg white and the serum of healthy children (or rabbits) artificially sensitized to egg white. The former group gives the Prausnitz-Küstner reaction, a positive complement fixation only in high dilutions of egg white, and an immediate cutaneous reaction, whereas the second group is said to give complement fixation also in low dilutions, a delayed intracutaneous skin reaction (never a cutaneous reaction), and no Prausnitz-Küstner reaction as far as sensitized rabbits are concerned. Although the antibody of anaphylaxis is known to be a precipitin, it is not decided if the same is true for the antibodies of allergies; e.g., to egg white, pollens, etc. The author feels that those antibodies are, if not identical, at least closely related to those in experimental anaphylaxis and perhaps distinguished only by a different physical state of the serum globulin in question. Of interest are substances called "dereagins" which are reported to inhibit or suspend the skin reactions to allergen injections. While the phenomena of anti-anaphylaxis are believed not to be due to a saturation of the antibodies in the cells but rather to an increase in histaminase or a temporary failure of the nervous system to react, the desensitization in treated

hay fever patients is explained by an exhaustion of cell antibodies. Albus found that the complement fixation titer dropped to a minimum in such patients who were treated until they were free from symptoms on exposure to pollens.

Two different explanations are offered for the Functional Disturbances in the Allergic Reactions. The physical theory of Doerr, the so-called membrane hypothesis, suggests that the antigen-antibody reaction is followed by formation of a primary stimulus consisting of a physical discharge on the cell proteins with subsequent disturbance of the optimal colloid state; the visible part of the allergic reaction represents the tissue response to that primary stimulus. The chemical theory holds that the tissue response is a consequence of the liberation of a histamine-like substance caused by the above-mentioned primary stimulus. In the author's opinion this chemical theory still lacks ultimate proof.

The monograph on Pathological Anatomy of the Allergic Reaction was written by Klinge, a pupil of Aschoff. He describes the histologic findings and relates his own experimental studies with the support of excellent photographs. Here we find the reasons why such diseases as arthritis, rheumatism, and endocarditis have been included in Berger's scheme of facultative allergy-determined diseases. In cases of allergic reactions which lead to a severe tissue injury, an acute or chronic inflammation may develop. Granulomas, i.e., cell nodules composed of histiocytes and giant cells, may be formed on an allergic basis, as in serum allergy and in rheumatism. The heart muscle is a preferred site of allergic inflammation characterized by interstitial granulomas. Injection of antigen in sensitized animals, either directly in the tissue or in the lymph vessels or in the blood stream, may bring on an allergic inflammation in any organ. Contrary to former opinions, it has been shown that intravenous injections of serum in sufficient amount into a sensitized animal provokes serious injuries to the vessel walls and the heart. If the animal survives, allergic inflammation of the coronary arteries, the heart valves, and the heart muscle can be demonstrated. Many experiments proved beyond doubt that the presence of antigen in the blood stream can produce allergic arteritis and carditis. Of interest are the reports on experiments which prove the localizing factors in allergy. The allergic reaction can be directed to certain tissues by various means; e.g., by local application of cold.

In another section the same author deals with allergy in infectious processes. He points out that a local tissue allergy and a generalized allergy toward bacteria and bacterial proteins have been proved to occur. The course of the typical infectious diseases with incubation period and development of immunity is influenced by bacterial allergy acquired during the incubation period. The infectious inflammations on the other side may rest upon an allergization which occurred without symptoms early in childhood. In recurrent or chronic infections, allergy toward certain soluble constituents of bacteria, such as tubercu-

lin, mallein, trichophytin, takes place, presenting typical histologic pictures. Infectious metastases and the phenomena of such chronic diseases as tuberculosis and syphilis can be explained on this basis. The allergic viewpoint provides in Klinge's opinion a better understanding of such diseases as rheumatism, periarteritis nodosa, endarteritis obliterans, endocarditis and phlebitis, and glomerulonephritis than the bacteriologic interpretation. Sensitization, alteration, and allergy are more momentous than the nature of the invading microorganism. In the author's terminology "rheumatic" means the altered tissue condition due to bacterial poison or antigen which brings on an allergic-hyperergic reaction with "Quellung" of the connective tissue and its consequences.

Hanhart (Zürich), the author of the monograph on Heredity and Constitution in Allergy succeeded in collecting a great number of large allergy-containing family trees and portrays some remarkable examples. He found in investigations of 70 large trees the general idiosyncratic predisposition to be transmitted as a Mendelian dominant. Of interest is a quotation from a study on 71 pairs of twins which demonstrated in identical twins 80 per cent concordance for hay fever, 60 per cent for migraine, and only 28.6 per cent for asthma. However, many family trees show a prominent organ determination of the allergic predisposition in that tree; e.g., explosive vomiting due to food in 3 generations, involving 6 of 21 members of the family; angioneurotic edema of the glottis in 3 generations resulting in death in 4 members of the family; on the other side, sensitivity to the same food in successive generations, e.g., to butter and cheese in 5 generations and to egg in 4 generations. In 34 family trees with more than 1,200 members 311 allergic persons were found of which 100 suffered from bronchial asthma. In 435 allergic families, with from 6 to 20 members each the author found 19 (4.3 per cent) cases of diabetes; in the families of several hundred diabetics a predisposition to allergy was entirely lacking. In his experience dislike of certain foods only suggests but does not prove an allergic hypersensitivity, and favored foods may act as allergens. While severe hay fever with pollen asthma, migraine, or food allergy may occur in well-balanced persons, bronchial asthma nearly always designates a neuropathic or psychopathic personality, but it is remarkable how many persons with an unstable autonomic nervous system present no allergic predisposition. The author draws the conclusion from his studies that the hereditary disposition is by far more important for the occurrence of idiosyncrasies than external influences, such as contact with allergens or general and local insults through inflammation, trauma, or intoxication.

Only some quotations shall be given from the section on Exogenous Allergens, written by Hansen. The most important fungi in Germany are *Aspergillus fumigatus, A niger, Penicillium glaucum,* rusts, and smuts. Frequently patients react only to the particular fungus growing in their own environment and not to spores obtained from other cultures.

Surprising and hard to explain is the statement that most of the reactions ascribed to house dust are caused by fungi in the dust, and that the author never saw a successful treatment with house dust extracts. To the volatile inhalation antigens belong the emanation of horses and particularly the ascaris antigen, an odd example of which is the case of urticaria in a mother disappearing when her child got rid of his round worms and reappearing after the child had a relapse. Sensitization to casein is believed to be frequent. In milk allergy, milk and all milk products, including cheese, should be omitted; boiled milk may be tried later on, but the author mostly observed relapses from it. Among 239 egg-allergic persons, 102 were sensitive to egg white, 61 to yolk, 76 to both. An important but often overlooked allergen is said to be honey. Food allergy is considered to be of greater importance than allergy to inhalants, and each case of inhalant allergy should be examined for food allergy as well. As to the contact antigens, poison ivy is found in Europe only in botanical gardens. Among 1,258 patients, the author had 17.25 per cent positive skin tests to ascaris antigen; Jadassohn found even 80 per cent. This result is explained by the very high frequency of ascaris infestation. It is estimated from stool examinations and findings in autopsies that in Europe 80 per cent of the whole population has had an ascaris infection some time in life. Loeffler's eosinophilic infiltrations in the lung can probably be explained by the migration of the larva through the lungs. Skin tests with ascaris extracts as well as such with echinococcus may remain positive long after elimination of the helminths.

In the section on *Special Diagnosis* Hansen numbers blood eosinophilia which exceeds 5 per cent at best among the probable signs of allergy. A more definite sign is eosinophilia in the secretion from the conjunctiva, nose, bronchi, colon, or vagina.

The scratch test has been almost entirely discarded by Hansen. The intracutaneous test is read after fifteen to thirty minutes and after six to twenty-four hours. In order to evaluate the reactivity of the skin, a test with salt solution and with histamine (1:10,000) is done in each case. The author lists twenty-one different tests which he does in the first sitting, a number of them group tests. Strangely enough, house dust, chocolate, and potato are not in this list. The immediate reaction is decisive, but positive delayed reactions are also evaluated. In patch testing the author dissolves the suspected antigen in water and then mixes it with glycerin ointment in various concentrations. He claims that this technique is superior because the antigen does not dry out and is more exactly confined to the skin area. In extracting the material for the intracutaneous test, he uses the technique of Frugoni with 12 per cent alcohol. Milk, egg white, and yolk are taken from fresh material for each testing and diluted with saline. Spores are extracted with Coca solution. Nitrogen content and pH are determined, but the author holds that standardization of the extracts according to nitrogen

content is of little value; the only satisfactory method so far is the testing of several normal persons with the new extract which must give negative reactions in concentrations of 1:100. Then the new extract is tested together with the well-known old one in a positive person. The author states that he cannot accept the observations in the American literature that skin tests sometimes fail in true allergic conditions. He claims that he had no failure in skin testing of gastrointestinal allergy and almost no failure in urticaria if of allergic origin. As to positive skin tests without corresponding clinical symptoms, they may indicate a sensitization biologically and clinically still beneath the threshold value; symptoms may develop in later years after the sensitization has increased. The inciting antigen may be lacking in the environment or the resorption may have become more difficult; e.g., in milk allergy. The skin reaction finally may designate a sensitization which has been overcome clinically; experience has shown that parenteral injection may produce shock in such a case.

Desensitization is reported to be particularly effective in allergy to pollens, fish, egg, milk, insulin, and liver extract. The author saw few or no results in allergy to fungi, animal hair, and feathers.

The particular conditions of exposure and resorption in man can explain the apparent discrepancies between clinical allergic reactions and classical anaphylaxis. Hansen, in the section on Clinical Evaluation of the Allergic Reaction, stresses the point that previous sensitization must always have occurred in allergic conditions although it may often be difficult to prove. The first contact may have been unnoticeably small or may have occurred by an uncommon route of invasion. An interesting example is the allergic reactions (asthma, urticaria, and eczema) seen in patients of a certain ward; skin tests and trial exposure could demonstrate these reactions to be due to inhalation of mercury used in inunction treatment of a patient of the same ward. Another possibility is the existence of an antigen nucleus common to various substances. Experiences and experiments allow the conclusion that shock following injection of horse serum may be due to sensitization to horse dander. The author has known well-analyzed cases of a common antigen nucleus in pollen and seed of the same plant, in egg and meat of hens, in serum and meat of horses, perhaps also in serum and milk of cows. He wonders if the frequent allergy to milk may be due to sensitization to cow serum following vaccination. Exposure frequently needs additional factors to be effective; e.g., injuries, hasty eating, deficiency of the digestive glands, disturbances of the liver function, promotion of absorption by coffee, or alcohol, or overfeeding. An example of the latter factor is the case of a quite normal young man who boasted to eat two dozen eggs in a challenge. He won, but he has suffered from urticaria and gastric symptoms following the ingestion of eggs ever since.

Interesting animal experiments are discussed which may give a clue to isolated allergic organ reactions. When, for instance an eye of a sen-

sitized animal has been bruised or has been artificially infected, the intravenous reinjection of the antigen given after the eye has healed results in an allergic reaction in that eye or in both eyes. Such experiments may explain the onset of an asthma due to foods following recovery from pneumonia and similar events. Other experiments demonstrate the important role of stasis and hyperemia and of the autonomic nervous system in the selection of certain organs in allergic reactions.

In the section on Drug Allergy positive passive transfer is reported in allergy to liver preparations. In one case of liver allergy skin tests 1:100,000 were strongly positive. Beside the liver extracts from cattle, pig, goat, and horse, extracts were also positive from guinea pigs, hens, and frogs in this same case; negative were all kinds of fish liver. The patch test apparently plays a more appreciated role in drug allergy in Europe than in this country. Mentioned are positive patch tests to mercury in cases of inhalation of mercury vapor with resulting scarlatiniform eruption and angioneurotic edema of the face, fever, and abdominal pain, and to quinine. Symptoms such as headache, pruritus, urticaria, and less often migraine or asthma, are said to be frequently due to tooth fillings with arsenic, formalin, iodoform, or thymol. It should be kept in mind that the aspect of the allergic reaction in drug allergy is influenced by the pharmacologic action of the drug and by the change in reactivity of the organism caused by the disease for which the drug is taken. The only safe explanation of thrombocytopenic purpura so far is drug allergy, resulting in an allergic reaction of the bone marrow with disturbance of thrombocyte production or resulting in a disturbance of the distribution of the thrombocytes. Nonthrombopenic purpura follows such drugs that act as dilators, or toxically on the capillaries; e.g., gold.

The absence of ragweed is the outstanding feature in European hay fever. Allergy to linden accounts for from 10 to 20 per cent of all hay fever cases. Allergy to beech, elm, and alder is very rare; hay fever due to the oak and pine tree was never seen by the author. Allergy to hazelnut, willow, and poplar is common. Allergy to goldenrod and lilac occurs, though rarely, and can always be traced to plants in the vicinity. As a consequence of an allergic pollen enteritis, larger amounts of food allergens are believed to be absorbed during the hay fever period; the hay fever symptoms, therefore, may be due partly to a concomitant allergy to foods. A latent allergy to milk or egg may cause a flare-up of an atopic dermatitis during the hay fever period. The author had favorable results with rush desensitization (Freeman), giving injections every two hours for two to five days and with rapid desensitization (daily injections for fourteen days); perennial treatment is highly recommended. Berger successfully desensitized by oral administration of pollens with addition of saponium purissimum (0.05 Gm.) for the purpose of promoting absorption. Severe reactions may

occur in oral desensitization. The disadvantage of the oral method lies in the uncertainty of how much of the pollen material is absorbed.

The section on Vasomotor Rhinitis (Baagoe) deals mainly with baker's rhinitis. In a survey of 300 bakers in 120 bakeries, 11 per cent were found to suffer from allergic rhinitis due to flour. Hansen found thymol as a constituent of face soap to be the cause of a vasomotor rhinitis of many years' duration; elimination produced immediate cure.

Berger defines asthma as a "multiple functional or functional inflammatory bronchiolar stenosis." He points out that stenosis and not spasm is the main characteristic. There must be a general predisposition of the tissue to respond to allergic or nonallergic stimulation and an increased special organ disposition. Sensitization may be favored by frequent and abundant exposure, by mechanical and chemical stimuli, by infections or injuries, or by neurohormonal factors. Among the causes of intrinsic asthma, tuberculosis is, in this author's opinion, of major importance either as an independent or an additional factor. He points to the experiments of Römer and others which could produce a fatal bronchiolar stenotic shock in tuberculous guinea pigs by injection or inhalation of tuberculoproteins. Periods of asthma may coincide with hematogenous spread of tuberculosis (proved by demonstration of tubercle bacilli in the blood stream). Asthma has been seen to develop following a tuberculous pleurisy or an early tuberculous infiltration in the lung. The therapeutic or provocative effect of tuberculin on asthmatics, particularly of the intrinsic type, is said to be often striking. The frequency of the different causes of asthma is estimated in the following order: (1) dust and feathers; (2) fungi; (3) bacteria; (4) hidden tuberculosis; (5) pollens; (6) foods, particularly egg, milk, wheat; drugs; (7) psychic and nervous causes. Only trial exposure and result of elimination can prove definitely which factor is responsible for the asthma.

Therapy deals with elimination and specific and unspecific desensitization. It is of interest that in Stockholm (Sweden) a special home for asthmatic school children has been founded. The author urges tuberculin treatment in all resistant cases of asthma which could not be relieved by allergen elimination. He was repeatedly able to terminate by this treatment periods of asthma that had resisted any other treatment for a long time. It should be started with a dilution of 10^{-15} or even $10.^{-18}$ In single cases the author had good results with liver extracts, cortin, and torantil. Pituitary extract is frequently given in combination with adrenalin; it seems to reinforce the adrenalin effect in many patients. The excellent effect of treatment with calcium in high doses is still maintained with reference to clinical observations and to the experimental work of Kallos who could inhibit anaphylactic inhalation asthma of guinea pigs for hours by administering calcium. Ten to 15 injections of calcium gluconate (10 to 20 per cent) are said to be frequently able to terminate asthma periods of long duration.

Orally, large doses are necessary (calcium lactate, 10 Gm. or 2 to 3 tablespoons daily). In respect to morphine, the author states, "The effect of the alkaloids is often miraculous indeed, and one would rather try these drugs than let an asthmatic patient suffocate." Of course, the dangers of addiction, of morphine allergy, and of paralysis of the respiratory center have to be kept in mind. (The author saw one asthma patient die in respiratory failure following morphine and oxygen administration.) Treatment with sulfur injections can be very effective. Severance of the bronchoconstrictor nerves was followed by relapses in the cases observed by the author. His feeling about surgical treatment is that the theoretic basis is not yet sufficiently understood and that the danger of the operation and the possibility of subsequent damage to the heart and the difficulties in locating the right nerves are other discouraging features. For chronic and resistant cases of asthma without clear etiology, the following order of therapeutic trials is recommended: (1) new work-up of the case; (2) fasting with building up of a careful diet; (3) tuberculin; (4) removal of foci of infection; (5) iodine plus arsenic medication; (6) sulfur or histamine or peptone; (7) autohemotherapy, vitamin C, liver; (8) purgative treatment; (9) fever therapy; (10) treatment in spas.

The section on Urticaria and Angioneurotic Edema gives instructive illustrations of the histology of the skin wheals. The urticarial wheal distinguishes itself from the wheal in skin tests with antigen through the lack of eosinophiles. Thirty minutes after intracutaneous injection of an antigen more than 50 per cent of the cells in the wheal are eosinophiles; a considerable migration of the cells from the capillaries into the tissue takes place. In the histamine wheal also an accumulation of eosinophiles is present after thirty minutes, but only within the capillaries. As to the physiology of urticaria, the author feels that the hemoclastic crisis of Widal is a typical criterion of the allergic reaction. It is characterized by drop of the blood pressure, drop in leucocyte count, decrease in protein colloids, increase in blood coagulability, sometimes rise in temperature, and albuminuria. In patients running a rapid course, closest attention and numerous studies are necessary for demonstrating the crisis, but even in skin testing the crisis appears. Besides the intracutaneous test, the patch test is often very helpful in diagnosis, particularly with contact antigens and drugs. If it fails, which happens rarely in the author's experience, passive transfer usually answers the question. In one most severe case of chronic urticaria with negative skin tests and negative history, passive transfer proved milk to be the causative factor. Elimination brought about complete cure. If complete elimination of a food factor is not feasible, desensitization has to be done. Many French writers had good results with intradermal injections given daily until the local reaction becomes negative and then advancing to a higher concentration of the antigen. Desensitization is said to be accomplished by this method commonly after 10 to 20 injec-

tions. The author mentions treatment with histamine given intracutaneously for urticaria of physical or psychic origin, but he has apparently no experiences of his own. He prefers in such cases also injections of 10 to 20 c.c. of calcium. In food urticaria he repeatedly had good results with administration of pepsin plus hydrochloric acid in large doses.

Opinions most divergent from the viewpoint of the American allergist, and probably also from a group of European dermatologists, are presented by Schreiner (Graz), the author of the section on Eczema. He comprehends epidermis and upper part of corium with the connective tissue of its vessels and its nerves as a functional unit and denies any necessity to break up the old concept of eczema, which is defined as an acute or chronic inflammation of the epidermis and cutis. There are only differences in intensity and pace of the process but no fundamental differences. Thus, the differentiation between atopic dermatitis and contact dermatitis is not drawn. In this connection it is worth mentioning that positive passive transfer has been accomplished in contact dermatitis due to milfoil and due to turpentine. The author states that the technique of Koenigstein-Urbach (with the contents of blisters) was sometimes successful when the original Prausnitz-Küstner method had failed. In the author's hospital the complement fixation test in cases of allergy to salvarsan, nickel, gold, mercury, and bromide has been employed with successful results.

The question of antigen resorption from the digestive tract is paramount for the problems of Gastrointestinal Allergy, and thus is extensively discussed. There are many factors which may influence the resorption; not each antigen ingestion therefore need result in an allergic reaction. The digestive ferments, the amount of antigen, its physical state (e.g., raw or cooked), the condition of the mucous membranes and finally the functions of the liver may play an important role. In the author's experience at least 30 to 40 per cent of all patients with stomach complaints suffer from allergic disturbances. All such symptoms as sense of fullness, slight pressure, belching, heartburn, vomiting, even hematemesis may be of allergic origin. X-ray examinations may be able to demonstrate the allergic gastritis. The barium meal of course must be free from antigen. In a case of extreme sensitivity to egg white (skin testing with 1:100,000 was followed by universal urticaria, angioneurotic edema of the face, and asthma) and positive skin tests to yolk and milk an x-ray examination of the stomach was quite normal. On the addition of one-sixth of an egg yolk to the barium meal nausea and vomiting occurred, the outlines of the mucosa pattern became very coarse, the pylorus was shut off, and the emptying time of the stomach was definitely delayed. The author believes that swelling of the mucous membranes, similar to angioneurotic edema or to an allergic gastritis, allergic pylorospasm, and hypermotility of the stomach are underlying the symptoms in antigen ingestion. He fully confirms the studies of Vaughan concerning the drop in leucocytes and

those of Squier and Madison concerning the rise of the eosinophiles following the antigen ingestion in such cases. Referring to a large experience in his hospital he states that a positive history of allergy and a manifest food allergy very often exist in ulcer patients. If the food allergy was present before the ulcer developed, the routine ulcer diet is without any results and not before an elimination diet has been started will the ulcer heal. Allergic spasm of the colon is probably more frequent that has been realized. Several interesting pathologic findings are reported in this section concerning patients who were erroneously operated upon for stomach ulcer, intestinal obstruction, and appendicitis. A localized angioneurotic edema due to an allergic reaction could be demonstrated in these cases; a subsequent analysis revealed the causative factor in two cases of intestinal obstruction to be salvarsan, and in one case of appendicitis, to be fish allergy. Indigestion and jaundice preceding urticaria or migraine are in the author's opinion, less likely to be allergic symptoms themselves but are due to a primary disturbance which facilitates the entrance of the antigen. No decision has been reached yet as to whether in human pathology the liver acts as a filter for antigens, under what circumstances this function may fail, and whether an allergic hepatitis occurs.

The section on Nervous System and Allergy discusses allergic reactions on the nervous system and the influence of the nervous system on reactions. In migraine, if there is an allergy, egg, milk, and chocolate are considered the main offenders; but inhalants, particularly pollens, occasionally are factors. Caffeine, 0.2 Gm., is the most important drug in the therapy of attacks. Of interest is the case history of a patient with recurrent erosions of the cornea and attacks of cerebral hyperesthesia of the entire right side of the body, including the right trigeminal and cochlear nerves and the left visual tract, due to vasospasm or localized angioneurotic edema, probably in the posterior part of the left inner capsule of the brain. Provocation of such an attack by skin testing with egg white, the success of elimination diet, and the prompt reappearance of severe attacks following experimental ingestion of eggs proved the allergic etiology. Neurologists often fail to diagnose angioneurotic edema within the skull as such. It may produce recurrent transient blindness due to edema of the optic nerve and retina; transient recurrent hemiplegias, cortical convulsions, perhaps also serous meningitis, encephalitis and myelitis, and finally recurrent paralysis of single cerebral nerves. Paralysis of peripheral nerves may occur not only in serum disease but has been seen to be also due to pollen inhalation. As to the psychogenetic origin of allergic attacks the author states that if attacks appear on psychical provocation without exposure to antigens, an antigen contact with allergic reaction must have occurred prior to this event; the subsequent reaction following psychogenic stimuli are comparable to the mechanism of a conditioned reflex and may become unspecific habitual reactions.

The ample work concerning the participation of the circulatory system in the allergic mechanism is thoroughly discussed in the chapter on Diseases of the Vessel and the Heart Based on Allergy. Besides arteriosclerosis, syphilis, rheumatism and others, allergic factors have to be considered in intermittent dysbasia. Allergic origin of angina pectoris has been reported by many writers; pollens, food (particularly meat), drugs, cresol, tobacco, bacteria, and toxins could be demonstrated to be factors by way of trial exposure and elimination diet. Knepper found positive skin tests and positive passive transfer tests to tobacco in 36 per cent of thirty-six patients with angina pectoris. Paroxysmal tachycardia has been believed to be of allergic origin in some cases. In one such case, honey and raisins could be proved to be the factors. Anaphylactic purpura has been observed very early. Moro as early as 1913 described two children with tuberculin purpura. Other causative factors in purpura have been foods or drugs such as salvarsan, gold, sedormid, insulin, and tetanus serum, and intrinsic antigens, such as menstrual substances. An interesting subject is the possibility of an allergic mechanism in the origin of glomerulonephritis which has been supported by ingenious animal experiments. The author cautions against premature acceptance of an allergic etiology of such conditions as Buerger's disease or periarteritis nodosa although we have to admit that such a possibility exists.

The results of numerous animal experiments and the occurrence of arthritis in serum disease of arthritis following tuberculin or vaccine injection, of arthritis during resorption of edema or effusions, and finally following ingestion of various foods, e.g., of pork or fish, strongly suggest an allergic share in the development of true rheumatism. Eleven points are presented by the author of the section on Allergies of the Joints as evidence of an allergic mechanism in rheumatic inflammation. Among them is the ample conformity in the anatomy of rheumatism and allergic diseases and the identity of the clinical aspect no matter which microorganism is involved, which is a characteristic feature of allergic reactions. The author makes this statement: "Rheumatic disease is the product of focus allergens mobilized by extrinsic or intrinsic causes, and of a rheumatic predisposition." Streptococci and tubercle bacilli play a prominent part as causative agents. From this statement follows that allergy and focal infection are only parts in the complex causes of true rheumatism.

It is known that gout cannot be explained exclusively as a disturbance of metabolism. Sudden onset, course, and type of symptoms in the joints suggested the comparison with anaphylactic events. The author points out that allergy is able to excite symptoms of gout but only if the purin metabolism has been disturbed; nonallergic causes such as histamine injections, leeches, and mosquito bites may also excite attacks. Important allergens are foods. In wine it is not the alcohol but egg

white or other albumins; furthermore, yeast proteins or bouquet substances may act as offenders. Bacterial allergens are also of importance.

The final chapter of the book has been written by Riehm who discusses the experimental work and clinical aspect of Allergic Conditions in the Eye. The theory of allergy to normal body tissue (autoanaphylaxis) which had been put forward in explaining some inflammatory diseases of the eye is considered to have been disproved, but body tissue, of course, may become an anaphylactogen after having lost its specific character. Some causes of allergic diseases of the eye are hairs of primrose, dust of wood or flour, spores, danders, feathers, and cosmetics. Foods, chemicals contained in food, and drugs are possible factors. Dorff saw three cases of allergic conjunctivitis due to ascaris antigen.

This review could present only selected points from the abundance of ideas and information which the book supplies. It has been attempted to give an impression of the broad approach of the work to its subject. To keep in mind that body tissue everywhere may be subject to an antigen-antibody reaction certainly means a definite progress in general medicine. In specific desensitizing therapy the German allergists seem to be far less successful than the American. The lower frequency of certain allergic conditions, e.g., the absence of ragweed hay fever, may have played a part in the failure to develop more effective and sufficiently individualized therapeutic methods.

Society Proceedings

To the Editor:

The Committee appointed by the Advisory of American Allergists to make a survey of the facilities for training in Allergy have carried out a most thorough investigation. It was the feeling of the Board that this report, which the Advisory Board has studied carefully, contains so much information of interest now and valuable for reference in the future that it should be made available to all. We therefore recommend its publication in the Journal of Allergy.
(Signed) The Advisory Board of American Allergists.

REPORT OF THE COMMITTEE ON POSTGRADUATE EDUCATION IN ALLERGY

To the Advisory Board of American Allergists:

The Joint Committee representing the Society for the Study of Asthma and Allied Conditions and the American Association for the Study of Allergy, appointed by you in the spring of 1940 to investigate the facilities available in this country for training in allergy, herewith submits its report.

Preliminary surveys of the institutions giving organized training in allergy were made by the members of this Committee in the respective districts which they were chosen to represent. Questionnaires were then forwarded to these organizations to elicit detailed information concerning their facilities for training. Each of the allergy clinics approved by the Advisory Board of American Allergists (formerly the Joint Committee of Standards) received a questionnaire. In addition, questionnaires were sent to other allergy clinics which came to the attention of the Committee. Questionnaires were also sent to individual members of both societies for the purpose of obtaining information on instruction given independently of organized allergy clinics.

The inquiries of the Committee were focused primarily on the opportunities for the training of specialists preliminary to their certification in allergy by the American Board of Internal Medicine.

The data obtained is summarized under three main headings: (1) facilities for training of residents, fellows, and graduate students; (2) allergy clinics with facilities for training in allergy; (3) miscellaneous facilities for training in allergy.

TABLE I

FACILITIES FOR TRAINING OF RESIDENTS, FELLOWS, AND GRADUATE STUDENTS IN ALLERGY

TITLE	INSTITUTION	CITY	UNIVERSITY	CHIEF OF SERVICE	YEAR POSITION WAS FOUNDED	REMUNERATION PER ANNUM	MAINTENANCE PROVIDED	TERM OF SERVICE IN YEARS	STARTING MONTH	SEPARATE ALLERGY WARD SERVICE	CLINIC SESSIONS PER WEEK	SPECIAL ALLERGY LABORATORY	NUMBER OF MEN TRAINED UP TO 1941	MISCELLANEOUS
Fellow	Children's Hosp.	Los Angeles		G. Piness	1934	$ 600	No	2	Jan. July	Yes	6	Yes	5	Part of time spent as assistant to chief in private office
Fellow in Med.	Johns Hopkins Hosp.	Baltimore	Johns Hopkins	L. Gay	1920	1,500	No	1	Sept.	No	3	Yes	5	Part time spent in general medicine
Research Fellow	Mass. General Hosp.	Boston	Harvard	F. Rackemann	1920	1,000 to 1,800	No	1 to 2		No	4	Yes	5	Not necessarily restricted to physicians
Research Fellow	U. Mich. Hosp.	Ann Arbor	U. Mich.	J. M. Sheldon	1937	1,500		2	July	No	6	Yes	3	
Resident	Jewish Hosp.	Brooklyn		M. Walzer	1935	300	Yes	1 to 2	July	Yes	4	Yes	4	
Fellow	N. Y. Postgrad. Hosp.	N. Y. C.	Columbia	W. C. Spain	1939	1,500	No	1	Nov.	Yes	3	Yes	1	
Graduate Student	N. Y. U. Col. Med.	N. Y. C.	N. Y.	A. Brown	1936	0	No	1	June	No	4	Yes	6	
Fellow	Roosevelt Hosp.	N. Y. C.		R. A. Cooke	1935	1,800 to 2,400	No	2 to 3		No	4	Yes	2	
Fellow	Asthma, Hay Fever and Allergy Foundation	Cleveland		M. Cohen	1937	900	No	1	July	No	6	Yes	2	
Fellow	Cleveland Clinic Foundation	Cleveland		J. W. Thomas	1941	500 to 1,500	Part	1	July	Yes	6	Yes	-	First year of service
Fellow	Jefferson Hosp.	Philadelphia		J. A. Clarke	1940	1,500	No	1	Oct.	No	2	Yes	1	
Fellow in Immunology	Med. Col. Va. Hosp.	Richmond	Med. Col. Va.	W. B. Blanton	1939	750	No	1	July	No	2	Yes	1	
Resident	Wisconsin Gen. Hosp.	Madison		W. A. Mowry	1940	900	Yes	1 to 2	July	No	-	Yes	-	First year of service

TABLE

ALLERGY CLINICS WITH FACIL

STATE	HOSPITAL	CITY	UNIVERSITY	CHIEF OF CLINIC	FOUNDED	TYPE OF CASE
				A. Clinics Approved by the Advis		
Cal.	Children's	Los Angeles		G. Piness	1922	Ped.
Cal.	Los Angeles County	Los Angeles		R. Lamson		Gen.
Cal.	Santa Fe Coast Lines	Los Angeles		R. Lamson		
D. C.	Children's	Washington	Geo. Washington	H. Donnally	1934	Ped.
Ind.	Ind. U. Med. Center (Riley Hospital for Child)	Indianapolis	Indiana	C. B. Bohner	1932	Ped.
Md.	Johns Hopkins	Baltimore	Johns Hopkins	L. N. Gay	1920	Gen.
Md.	University	Baltimore	Maryland	H. Bubert		Gen.
Mass.	Beth Israel	Boston		A. Colmes	1930	Gen.
Mass.	Mass. General	Boston	Harvard	F. Rackemann	1920	Gen.
Mich.	University	Ann Arbor	U. Mich.	J. M. Sheldon	1927	Gen.
Minn.	Mayo Clinic	Rochester	U. Minn.	L. E. Prickman		Gen.
Mo.	Barnes	St. Louis	Washington	C. H. Eyerman	1916	Gen.
Mo.	Firmin Desloge	St. Louis	St. Louis	E. Moore	1933	Gen.
Mo.	McMillan	St. Louis		F. K. Hansel		
N. J.	Mountainside	Montclair		C. Weston	1926	Gen.
N. Y.	Beth El	Brooklyn		H. Markow	1932	Gen.
N. Y.	Jewish	Brooklyn		M. Walzer	1921	Gen.
N. Y.	Children's	Buffalo	U. Buffalo	V. Cohen	1932	Ped.
N. Y.	Buffalo General	Buffalo	U. Buffalo	H. Osgood	1927	Gen.
N. Y.	Bellevue H. 3rd	N. Y. C.	N. Y.	A. Brown		Gen.
N. Y.	Bellevue Child	N. Y. C.	N. Y.	S. Bell		
N. Y.	Beth Israel	N. Y. C.		L. Sternberg	1926	Gen.
N. Y.	French	N. Y. C.		T. Vina	1914	Gen.
N. Y.	Gouverneur	N. Y. C.		H. Gelfand	1931	Gen.
N. Y.	Lebanon	N. Y. C.		C. Spivacke	1924	Gen.
N. Y.	Midtown	N. Y. C.		A. Brown		Gen.
N. Y.	Mt. Sinai	N. Y. C.		J. Harkavy	1926	Adult
N. Y.	Mt. Sinai	N. Y. C.		M. Peshkin	1920	Ped.
N. Y.	New York	N. Y. C.	Cornell	H. Baldwin	1932	Adult
N. Y.	New York	N. Y. C.	Cornell	H. B. Adams	1932	Ped.
N. Y.	N. Y. Eye and Ear	N. Y. C.		J. H. Barnard	1937	Gen.
N. Y.	N. Y. Infirm. Women and Children	N. Y. C.		L. Claman	1936	Gen.
N. Y.	N. Y. Polyclinic	N. Y. C.		M. Harris	1928	Gen.
N. Y.	N. Y. Postgrad.	N. Y. C.	Columbia	W. C. Spain	1920	Adult
N. Y.	N. Y. Postgrad., Ped.	N. Y. C.	Columbia	R. Chobot	1929	Ped.
N. Y.	N. Y. Skin & Cancer	N. Y. C.	Columbia	M. Sulzberger		Derm.
N. Y.	Roosevelt	N. Y. C.		R. Cooke	1932*	Gen.
N. Y.	St. Luke's	N. Y. C.		W. Tucker	1921	Gen.
N. Y.	Sydenham	N. Y. C.		A. H. Fineman	1928	Gen.
N. Y.	Strong Mem. & Rochester Municipal	Rochester	U. Roch.	S. Bullen	1926	Gen.
N. Y.	Rochester Gen.	Rochester		N. Francis	1925	Gen.
N. Y.	Syracuse Free Disp.	Syracuse	Syracuse	J. Wiseman		

II

ITIES FOR TRAINING IN ALLERGY

NEW CASES IN 1940	SESSIONS PER WEEK	AVERAGE CENSUS PER SESSION	AVERAGE NUMBER OF PHYSICIANS PER CLINIC SESSION	TOTAL NUMBER OF STAFF PHYSICIANS	INDIVIDUAL CASE MANAGEMENT	SPECIAL ALLERGY LAB.	ALLERGY TECHNICIANS		ADEQUACY OF LAB. FACILITIES	MISCELLANEOUS
							PART TIME	FULL TIME		
ory Board of American Allergists										
250	4	135	4	4	Ind.	Yes	1	4	Comp.	Total patients (1940), 968; total visits (1940), 13,337
200	2	35	3-4	5	Ind.	Yes	1		Adeq.	No statistics available
	1	18	1	1		No			Adeq.	Assisted by resident
900	3	115	11	18	Div.	Yes			Comp.	
187	4	30	3	9	Ind.	Yes		1	Adeq.	
264	2	65	6	7	Ind.	No		1	Adeq.	
1,000	4	110	4	12	Div.	Yes	2	1	Comp.	
	6	60	4		Div.	Yes	2	1	Adeq.	
	6			6	Ind.	Yes			Comp.	
110	2	19	8	8	Ind.	Yes			Comp.	
64	2	15	2	2	Div.	Yes		1	Comp.	
48	1	65	4	4	Div.	No			Inc.	No statistics available
130	2	60	7	8	Div.	Yes	1		Adeq.	
433	4	125	10	13	Ind.	Yes		2	Comp.	
32	2	37	2-3	4	Div.	Yes	1		Adeq.	
119	2	47	5	6	Div.	No			Adeq.	
	2			3	Ind.	No	0	0	Inc.	No statistics available
214	3	50	3	7	Ind.	Yes	0	0	Adeq.	
237	2	160	7	7	Ind.	Yes	1	2	Comp.	
454	3	62	4	8	Div.	No	1		Inc.	
185	3	75	9	11	Ind.	Yes			Comp.	
	2	50	3	4	Ind.	No	0	0	Inc.	
339	3	195	12	12	Ind.	Yes		1	Comp.	
200	3	90	14	15	Ind.	Yes			Comp.	
567	5	55	4	14	Ind.	Yes			Comp.	
200	2	50	6	10	Ind.	Yes			Comp.	
179	3	30	1	1	Div.	No			Adeq.	Assisted by interne
142	1	45	4	4	Ind.	No			Inc.	
35	3	32	3	7	Ind.	Yes			Adeq.	
335	3	150	14	18	Div.	Yes		2	Comp.	
109	1	90	10	11	Ind.	Yes			Comp.	
	12		3		Ind.	Yes		2	Comp.	
588	4	200	9	18	Ind.	Yes		3	Comp.	*Founded at N. Y. H., 1916
201	2	47	4	4	Ind.	No		1	Adeq.	
111	4	35	4	5	Div.	No			Inc.	
177	2	30	4	7	Div.	No			Inc.	
270	2	35	2	4	Div.	No			Adeq.	
				6						No statistics available

TABLE

STATE	HOSPITAL	CITY	UNIVERSITY	CHIEF OF CLINIC	FOUNDED	TYPE OF CASE
Pa.	Children's	Philadelphia	U. Pa.	S. C. Copeland		Ped.
Pa.	Germantown	Philadelphia		J. A. Clarke	1921	Gen.
Pa.	Grad. Hosp., Univ. Pa.	Philadelphia	U. Pa.	H. Wilmer		
Pa.	Hosp. Univ. Pa.	Philadelphia	U. Pa.	R. Kern	1920	Gen.
Pa.	Jefferson	Philadelphia	Jefferson	J. A. Clarke	1921	Gen.
Pa.	Mt. Sinai	Philadelphia		G. Blumstein	1928	Gen.
Pa.	Pennsylvania	Philadelphia		J. McLaughlin		Gen.
Pa.	Temple U.	Philadelphia	Temple	L. Tuft	1931	Gen.
Pa.	Univ. Pittsburgh	Pittsburgh	U. Pitts.	L. Criep	1924	Gen.
Pa.	U. S. Veterans	Pittsburgh		L. Criep	1926	Gen.
R. I.	Rhode Island	Providence		W. P. Buffam	1925	Gen.
Va.	Med. Col. Va.	Richmond	Med. Col. Va.	W. Blanton	1937	Gen.

B. Clinics Not Yet Passed Upon by the

Cal.	U. California	San Francisco	U. Calif.	W. C. Deamer		Ped.
Ill.	Northwestern U.	Chicago	Northwestern	S. M. Feinberg	1923	Gen.
Ill.	U. Ill. Res.	Chicago	Illinois	B. Z. Rappaport	1928	Gen.
Mass.	Boston Dispensary	Boston	Tufts	E. A. Brown		Gen.
Mass.	Children's	Boston	Harvard	H. N. Pratt		Ped.
Mass.	Children's	Boston	Harvard	L. W. Hill	1929	Ecz.
Mass.	Mass. Memorial	Boston		F. C. Lowell	1920	Gen.
Mich.	Children's	Detroit		S. Levin	1926	Ped.
Mo.	St. Luke's	St. Louis		L. P. Gay	1936	Gen.
Neb.	University	Omaha	U. Neb.	E. MacQuiddy	1936	Gen.
N. Y.	Albany	Albany	Union	L. Gorham	1928	Gen.
N. Y.	Lincoln	N. Y. C.		H. Shahon	1938	Gen.
N. Y.	N. Y. U. Clinic	N. Y. C.	N. Y.	A. Brown		Gen.
N. Y.	Stuyvesant Polycl.	N. Y. C.		H. Gelfand	1929	Gen.
Ohio	Cincinnati Gen.	Cincinnati	U. Cincinnati	A. R. Zoss	1933	Gen.
Ohio	Cleveland City	Cleveland	Western Res.	W. P. Garver	1933	Gen.
Ohio	Cleveland Clinic	Cleveland		J. W. Thomas	1921	Gen.
Ohio	St. Alexis	Cleveland		M. Cohen	1934	Gen.
Ohio	Children's	Columbus	Ohio State	W. F. Mitchell	1941	Ped.
Ohio	Ohio S. U. H.	Columbus	Ohio State	J. A. Michell	1934	Adult
Ore.	Oregon Med. School	Portland	U. Oregon	R. L. Benson	1935	Gen.
Va.	U. Virginia	University	U. Virginia	O. Swineford	1931	Gen.

II—CONT'D

NEW CASES IN 1940	SESSIONS PER WEEK	AVERAGE CENSUS PER SESSION	AVERAGE NUMBER OF PHYSICIANS PER CLINIC SESSION	TOTAL NUMBER OF STAFF PHYSICIANS	INDIVIDUAL CASE MANAGEMENT	SPECIAL ALLERGY LAB.	ALLERGY TECHNICIANS		ADEQUACY OF LAB. FACILITIES	MISCELLANEOUS
							PART TIME	FULL TIME		
240	2	35	2	2	Div.	Yes			Inc.	
148	2	33	3	4	Ind.	No			Inc.	No statistics available
292	2	70	5	10	Div.	Yes	2	1	Comp.	
450	3	100	9	18	Div.	Yes		3	Adeq.	
75	2	30	3	8	Div.	No			Adeq.	
185	2	40	3	3	Div.	No			Inc.	
381	2	75	6	6	Div.	Yes		1	Adeq.	
200	1	200	6	5	Div.	No	0	0	Adeq.	
120	4	12	2	2	Ind.	Yes		1	Comp.	
167	3	30	3		Ind.	No	0	0	Inc.	Separate adult and pediatric clinics
172	2	37	5	6	Div.	Yes		1	Adeq.	
Advisory Board of American Allergists										
	3	13	1	1	Div.	No	2		Adeq.	Assisted by resident and interne
300	2	70	5	9	Div.	Yes	1		Comp.	
	4	50	4	8	Ind.	No	1		Adeq.	
425	2	165	8	12	Div.	Yes	3		Adeq.	
300	2	60	3	3	Ind.	Yes	1		Adeq.	
150	1	15	1	1	Ind.	No	1		Inc.	
56	2	40	3	3	Div.	Yes	4		Adeq.	One in winter
150	2	60	3	3	Ind.	No			Adeq.	
20	2	35	1	1	Div.	No		1	Inc.	Assisted by interne
55	2	8	1	1	Div.	No			Inc.	Assisted by student
99	3	45	2	2	Div.	Yes	1		Adeq.	Two in winter
20	2	65	5	6	Div.	No			Inc.	
	3		4	8	Ind.	Yes			Comp.	
135	3	40			Div.	No			Inc.	
200	3	65	3	4	Ind.	Yes			Adeq.	
197	1	98	3		Div.				Inc.	
250	6	45	2	4	Div.	Yes	2	4	Comp.	
30	1	20	3		Div.	No				
	?		1	1	Ind.	No	1		Inc.	New clinic
140	1	26	2	3	Div.	Yes	1		Adeq.	
	2		1	3		Yes		1	Adeq.	
	1	25	2	2	Ind.	Yes	1	1	Adeq.	

TABLE

INTENSIVE POSTGRADUATE

HOSPITAL	CITY	AUSPICES	DIRECTOR	TUITION
Cook County	Chicago	Cook County Grad. School Med.	L. Unger	$200
Cook County	Chicago	Cook County Grad. School Med.	S. J. Taub	200, 1 mo. 500, 6 mo.
Boston Disp.	Boston	Tufts Med. School	E. A. Brown	25
Mass. General	Boston	Harvard and Am. Col. Phys.	F. M. Rackemann	50
University	Ann Arbor	U. Mich.	J. M. Sheldon	15
Barnes	St. Louis	Washington U. and Am. Col. Phys.	H. L. Alexander	45
Mt. Sinai	N. Y. C.	Columbia	J. Harkavy	35
N. Y. Postgrad.	N. Y. C.	Columbia	W. C. Spain	150
N. Y. Postgrad., Skin & Cancer	N. Y. C.	Columbia	M. Sulzberger	50 75
Roosevelt	N. Y. C.	Am. Col. Phys.	R. A. Cooke	45

*Intensive courses of thirty-five or more hours, omitting short elementary courses and or otolaryngology.

While making this survey, the attention of the Committee was called to various short introductory courses which are available to the general practitioner and internist for intensive instruction in allergy. Because of their possible interest to the medical profession, they have also been included in this report.

Respectfully submitted,

Matthew Walzer, M.D., Chairman
Harvey Black, M.D.
Samuel Feinberg, M.D.
George Piness, M.D.
Francis M. Rackemann, M.D.
William B. Sherman, M.D.
Walter L. Winkenwerder, M.D.

III

COURSES IN ALLERGY*

NUMBER OF INSTRUCTORS	DURATION OF COURSE IN WEEKS	HOURS PER WEEK	TOTAL NUMBER OF HOURS	TYPE OF INSTRUCTION			CLASS LIMITED TO	NUMBER OF REGISTRANTS IN 1940	MISCELLANEOUS
				LECTURES	CLINICAL	LABORATORY			
4	4	48	200	x	x	x	3	3	
1	4	48	192	x	x	x	3		
1	26	48		x	x	x	2		
	1	25	25	x	x		8	13	Elementary course
	1	26	26	x	x		8		Advanced course
10	1½	48	60	x	x	x	6	6	
10	1	35	35	x	x		25	27	
12	2		96	x	x	x	8		To be offered in 1942
	8	12	72	x	x	x	12	3	Special additional course on physicochemical aspects of allergy by Abramson; eight afternoons
10	4		105-140	x	x	x	10	15	Given twice yearly
3	13		24	x					Dermatologic allergy
3	13		78		x		5		Dermatologic allergy
14	2	48	96	x	x	x	8	8	

lectures on allergy given as part of postgraduate courses in general medicine, pediatrics,

MISCELLANEOUS FACILITIES FOR TRAINING IN ALLERGY

A. An apprenticeship for one year is offered by W. T. Vaughan and W. B. Graham of Richmond, Va. It includes organized instruction in diagnosis and treatment, laboratory training, and research. Remuneration is given.

B. Individual instruction in practical and theoretical aspects of allergy for periods ranging from two to six months is offered by Milton B. Cohen, Cleveland; R. W. Lamson, Los Angeles; B. Z. Rappaport, Chicago; H. B. Wilmer and M. M. Miller, Philadelphia; and Samuel Feinberg, Chicago; and others. There is usually a tuition fee for such courses of instruction which are given at the hospital clinics and at the offices of the instructors.

There are undoubtedly other opportunities available throughout the country for individual instruction, but information concerning these positions has not been given to the Committee on Postgraduate Education in Allergy.

REPORT OF THE COMMITTEE ON A POLLEN SURVEY OF THE UNITED STATES, THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

At the 1940 spring meeting of the Society, the following committee was appointed to make a pollen survey of the United States: Doctors VanderVeer (chairman), Barnard, Cunningham, Nelson, Pratt and Simon. The committee realized that extensive and important surveys made by a few individuals were available but desired to assemble data from its members. Accordingly, questionnaires were sent to all members of the Society. Of those returned, sixty-four contained relevant information. It was assembled and analyzed.

Despite differences of opinion both concerning the quantitative and qualitative prevalence of certain pollens in given localities, a considerable amount of interesting information was revealed. Since the survey will take long to complete, it was voted at the spring meeting in 1942 to publish in this JOURNAL a few of the assembled statistics at this time as a preliminary record. As further data become available, they will be similarly presented.

THE EDITOR.

TABLE I

IMPORTANT POLLENS

From Table IV

TREES		GRASSES		RAGWEED	
Oak	35	Timothy	39	Amaranthus	6
Elm	23	Orchard	18	Marsh elder	5
Maple	19	Red top	13	Chenopod	5
Birch	18	June	13	Cocklebur	5
Ash	11	Sweet vernal	6	Mugwort	4
Poplar	11	Bermuda	4	Sage	2
Sycamore	11	Johnson	4	Thistle	2
Hickory	9	Bluegrass	4	Mesquite	2
Beech	7	Rye	3	Goldenrod	1
Alder	6	Velvet	1	Hemp	1
Cedar	4	Plantain	26		
Cottonwood	4	Sorrel	6		
Pecan	4	Sedge	1		
Walnut	4	Dandelion	1		
Hazel-Willow	1	Mayweed	1		
Pine asper	1	Corn	1		
Chestnut caddis fly	1	Wheat	1		
		Oats	1		
Bayberry mulberry	1	Alfalfa	1		
Acacia	1				

TABLE II

MOLDS

From Table IV

MOLD	*Order of Importance*			
	FIRST	SECOND	THIRD	OTHERS
Alternaria	44			
Hormodendron		20	2	
Aspergillus		5	6	3
Penicillium		2	3	6
Monilia albicans	1 (Florida)	1		3
Cladosporium		2		
Fusarium				4
Helminthosporium		1	2	2
Mucor			2	1
Dematium			2	1
Cephalothecium		1		1
Grain smuts				3
Phoma		1		1
Rhizopus				2
Macrosporon			1	
Yeasts				1
Tricoderma				1
Acrothecium				1
Chaetomium				1

TABLE III

POLLEN-FREE AREAS

From Table IV

California	Downtown San Francisco and Oakland
Canada	Province of Ontario, wooded sections; also above Minnesota; Isle Royale and Belle Islands
Colorado	Leadville, Georgetown, Idaho Springs, all at altitude of 8,000 to 10,000 feet
Florida	East Coast
Maine	Northern part and Eastern part
Mexico	Mexico City
Michigan	Upper Peninsula and upper part of lower Peninsula
New Hampshire	White Mountains
New Jersey	Atlantic City, for mold cases; also tree and grass season
New York	Fire Island, Central Adirondacks, Montauk Point
North Carolina	Mountain section
Northern Michigan	Wisconsin and Minnesota, Mackinac Island, Washington Island in Lake Michigan, North Shore of Lake Superior, Arrowhead Region of Northern Minnesota
Oregon	Mount Hood area
Texas	Gulf Coast

TABLE IV

ASSEMBLED DATA FROM RETURNED QUESTIONNAIRES

LOCATION NAME	MOLDS	POLLENS	SEASON	POLLEN-FREE AREAS
Calif. (Oakland) A. H. Rowe	None	Acacia, oak, sycamore, Poa annua, oats, bromus carinatas	Jan. to April	Downtown San Francisco and Oakland
		Festuca myuros, Hordeum vulgare	Jan. to May	
		Lolium perenne (++)	May to July	
		Bermuda grass	May to Nov.	
		Sage (++), mugwort	July to Nov.	
		Amaranthus, Atriplex, Salicornia, western ragweed	Aug. to Nov.	
Colo. (Denver) Cunningham	None	Russian thistle, pigweed, chenopod	July to Sept.	Leadville, Georgetown, Idaho Springs
		Sage	Mid-July to Mid-Sept.	
		Kochia, ragweed	Aug. 1 to Sept. 15	
		Iva	Aug. 20 to Oct. 1	
Dist. of Col. (Washington) Bernton	*Important* Alternaria Cladosporium Aspergillus	Trees Grasses, plantain Ragweed	Feb. 22 to June 1 Mid-May to Mid-July Mid-Aug. to Frost	None
Dist. of Col. (Washington) G. T. Brown	*Important* Alternaria Aspergillus Mucor Grain smut Fusarium Penicillium	Oak, hickory, walnut, pecan, birch, elm, mulberry, sycamore, ash, maple, cottonwood, cedar	March, April, May	None
		Timothy, red top, orchard grass, June, sweet vernal, rye grasses	Mid-May to Mid-July	
		Plantain	Mid-May to Aug. 1	
		Ragweed, cocklebur, sage, mugwort, goldenrod	Mid-Aug. to Oct. 1	

Fla. (Tampa) Metzger	*Occasionally important* Alternaria Monilia Trichophytes Claudisporium	Eucalyptus Pecan, oak Bayberry Citrus trees, pine, cypress, Spanish moss Bermuda, St. Augustine, centipede grasses Low ragweed	Feb. and March End Jan. to April March and April Of no importance Late Feb. to April and June and early July; some pollen all year Mid-Aug. to Mid-Nov.; maybe even early May	East coast of Florida Beach
Ga. (Atlanta) Davison	None	Alder, elm, cottonwood, oak, pecan, pine, hickory, grass, ragweed, chenopod	Tag alder, Jan. 18	Mountains of North Carolina
Ga. (Atlanta) Lowance	None	Ragweed		East coast of Florida, Mountins of North Carolina
Ill. (Chicago) Feinberg	*Important* Alternaria Hormodendron Helminthosporium Acrothecium Penicillium Phoma Chaetomium Monilia Cephalosporium Smuts Fusarium	Oak, elm, maple, cottonwood, ash, walnut June, orchard, red top, timothy grasses, ragweed, Russian thistle	March 25 to June 1 Aug. 1 to Sept. 25	Northern Michigan, Minnesota, Wisconsin; Ontario, Isle Royale, Belle Isle
Ill. (Chicago) Hecht	*Important* Alternaria Aspergillus	Grasses, ragweed		None
Ill. (Chicago) Unger	*Important* Alternaria Hormodendron Helminthosporium	Trees, grasses, ragweed		None

TABLE IV—CONT'D

LOCATION NAME	MOLDS	POLLENS	SEASON	POLLEN-FREE AREAS
Ill. (Evanston) Nelson	*Very important* Alternaria Hormodendron Penicillium Aspergillus Rhizopus	Ash, cottonwood, maple, elm, oak Bluegrass, timothy, red top, orchard grasses Ragweed, burweed, marsh elder	March 15 to June 1 May 30 to July 20 Aug. 15 to Oct. 1	Northern Wisconsin, Mackinac Island, Washington Island (Lake Michigan), Canada North of Port Arthur
Ind. (Indianapolis) Clowes	*Occasionally important* Alternaria	Ragweed		None
Ky. (Louisville) Simon	*Important* Alternaria Hormodendron	Oak, maple, walnut, sycamore, elm, ash Bluegrass, red top, orchard, timothy grasses Ragweed	Variable Early May to late June Mid-Aug. to late Sept.	None
Md. (Baltimore) Fink	*Important* Alternaria	Oak, elm, sycamore, beech Grasses Ragweed	April 25 to May 15 May and June Aug. 15 to Sept. 20	None
Md. (Baltimore) Furstenberg	*Some importance* Alternaria	*See* Fink		
Md. (Baltimore) Gay	*Important* Alternaria Aspergillus Hormodendron Helminthosporium	Oak Timothy, orchard grasses Plantain Ragweed	April 25 to May 10 May 8 to Aug. 1 May 15 to Aug. 15 Aug. 8 to Oct. 15	None
Md. (Baltimore) Herman	*Rarely important* Alternaria	Oak, elm, maple, beech Timothy, orchard grasses Plantain, ragweed	March 20 to May 10 May 20 to July 10 June 1 to Sept. 1	None
Md. (Baltimore) Winkenwerder	None	Trees Grasses Ragweed	March 15 to May 15 May 10 to July 1 Aug. 10 to Sept. 30	None
Mass. (Boston) Brown, E. A.				None

Mass. (Boston) Burrage	*Important* Alternaria Hormodendron	Elm, oak, birch Timothy, red top, orchard grasses Ragweed	Early to late May June 1 to Mid-July Mid-Aug to Frost	None
Mass. (Boston) Colmes	*Important* Alternaria Hormodendron	Oak, birch, ash, alder, elm, poplar, willow Grasses, plantain Ragweed	April to June June to August Aug. to Oct.	White Mountains
Mass. (Boston) Pratt	*Very important* Alternaria Hormodendron Dematium	Elm, birch, oak June, timothy, red top, orchard, sweet vernal grasses Ragweed, cocklebur	April 23 to May 25 June 1 to July 15 Aug. 20 to Oct. 1	North Maine, White Mountains
Mass. (Boston) Rackemann	*Important*	Birch, oak Timothy, red top, orchard grasses Ragweed	May June Aug.	East Maine, New Hampshire
Mich. (Ann Arbor) Sheldon	Alternaria Hormodendron Penicillium	Maple, elm June grass Timothy Ragweed	Mid-April to late June Mid-May to July 1 Late June to Aug. 5 Aug. 14 to Sept. 25	Upper peninsula of Michigan and upper part of lower peninsula
Mich. (Detroit) Waldbott	*Important* Alternaria Smut rust Penicillium Monilia Yeast	Willow, oak, elm, pine, Johnson, timothy, orchard grasses, plantain, ragweed Reprint to be published	Usual seasons	Northern Michigan, North of Sault Ste. Marie
Minn. (Minneapolis) Wittich	*Important* Alternaria Hormodendron Aspergillus Penicillium Mucor Helminthosporium Fusarium Wheat bunts Corn smut Sorghum Grain smuts	Elm, maple, birch, hazel, poplar, willow Sedge, bulrush, cattail, ash, oak Grass Walnut, butternut, hickory Plantain Dock sorrel Alfalfa, clover Pigweed, Russian thistle Sage wormwood Ragweed	April to May April to Mid-August Mid-April to Mid-May Mid-May to Mid-Sept. Mid-May to early June June to July End of May to early Sept. June to Sept. Mid-June to Mid-Sept. July to Mid-Oct. Early Aug. to Oct.	Lake Superior, Northern Minnesota

TABLE IV—CONT'D

LOCATION NAME	MOLDS	POLLENS	SEASON	POLLEN-FREE AREAS
Minn. (Rochester) Prickman	Rarely important	*See* reprints, Ellis and Rosendahl		North shore of Lake Superior, Northern Minnesota
Mo. (St. Louis) Eyerman	Uncertain: Alternaria Hormodendron	Elm, maple Oak Grasses Ragweed	March to early April April 15 to June 1 June and July Mid-Aug. to Oct.	None
N. J. (East Orange) Schaffer	*Important* Alternaria Hormodendron Aspergillus Penicillium	Oak, chestnut, maple, elm, birch Timothy, sweet vernal, orchard grasses Marsh elder, ragweed, plantain	April and May June to early July Mid-Aug. to Frost	None
N. J. (Glen Ridge) Weston	Uncertain	Trees, plantain, corn Ragweed		None
N. J. (Montclair) Alford	No experience	Alder, aspen, elm, hickory, oak, birch poplar, beech, maple, sycamore, ash, pine, timothy grass, plantain, ragweed		None
N. J. (Morristown) Beaver	*Important* Alternaria c̄ L.H.F. Tricophytin c̄ infection Monilia?	Same as New York		None
N. Y. (Albany) Counse	*Important* Alternaria Hormodendron	Maple, elm, birch, oak, beech, poplar Timothy, sweet vernal, June, red top, Bermuda grasses Ragweed	Early March to Mid-May May 30 to July 30 Mid-Aug. to early Oct.	Adirondacks
N. Y. (Buffalo) Arbesman	*Important* Alternaria Hormodendron	Elm Timothy Ragweed	May 10 to June 1 June 10 to July 15 Aug. 18 to Sept. 28	None

N. Y. (Buffalo) Osgood	*Occasionally* Alternaria Penicillium Hormodendron Rhizopus	Elm, oak, poplar, beech, birch, ash, maple Timothy and other grasses, plantain. sorrel Ragweed Caddis fly	April and May May 20 to end of July Mid-Aug. to end of Sept. June 5 to Sept. 15	Shores of Lake Erie, Great Lakes Caddis fly, four to five miles from Niagara River
N. Y. (Ithaca) Berresford	*Important* Alternaria Hormodendron Mucor Penicillium	Birch, beech, oak, alder, elm, ash. poplar, hickory, timothy grass, sorrel, plantain Ragweed, cocklebur, chenopod	End of May to Mid-July Mid-Aug. to Oct.	Northern Adirondacks
N. Y. (Rochester) Bullen	*Important* Alternaria Monilia Aspergillus	Oak, elm (rare), maple Timothy, orchard grasses Ragweed (short more than giant)	Late April to late May Early June to Mid-July Mid-Aug. to Frost	Central Adirondacks, Ontario
N. Y. (Rochester) Glaser	Undecided	Maple, oak, elm, poplar June, orchard, red top, timothy Low ragweed (no giant here)	April to May Early May to Aug. 1 Aug. 15 to Frost	Adirondacks
N. Y. (Syracuse) Wiseman	Not much experience	Oak, walnut, poplar, elm, willow, ash, grasses, plantain, sorrel Ragweed	End of May to late July Mid-Aug. to Frost	None
N. Y. (Brooklyn) Grolnick	Uncertain	Timothy Ragweed	End of May to July 10 Aug. 10 to Sept. 20	None
N. Y. (Brooklyn) Walzer	None			Montauk Point, L. I.
N. Y. (New York) Bell	*Important* Alternaria Cephalothecium Dematium	Alder, birch, oak, bayberry Plantain Sorrel Grasses Ragweed Marsh elder	March 25 to June 1 May 3 to Aug. 15 May 3 to July 1 May 25 to July 20 Aug. 10 to Oct. 1 Aug. 15 to Sept. 15	Fire Island, Central Adirondacks
N. Y. (New York) A. Brown	*Occasional* Alternaria	Trees Timothy and plantain Ragweed	April to October	None

TABLE IV—CONT'D

LOCATION NAME	MOLDS	POLLENS	SEASON	POLLEN-FREE AREAS
N. Y. (New York) Chobot	*Rarely* Alternaria Aspergillus	Trees Grasses Ragweed	 April 15 to Sept. 20	Montauk Point, L. I.
N. Y. (New York) Fineman	*Occasionally* Alternaria Aspergillus	Oak, birch, poplar, hickory, maple, sycamore Timothy, red top, orchard, June grasses Ragweed	March 15 to May 10 Mid-May to July 20 Aug. 15 to Oct. 10	Fire Island, Central Adirondacks, New Hampshire
N. Y. (New York) Loveless	*Occasionally*	Birch, oak, hickory, beech, elm Timothy Plantain Ragweed	April 10 to May 7 June 15 to July 15 June 15 to Oct. 1 Aug. 15 to Oct. 1	White Mountains
N. Y. (New York) Shanon	None	Alder, elm, poplar, birch, beech, ash, walnut, hickory, sweet vernal, June, red top, orchard, timothy grasses Cocklebur, ragweed	March 22 to July 16 Early Aug. to end of Sept.	None
N. Y. (New York) Thomas	*Rare* Alternaria Penicillium	Timothy Ambrosias	June 20 to Aug. 1 Aug. 15 to Frost	None
N. Y. (New York) VanderVeer	*Important* Alternaria Aspergillus Hormodendron Monilia Penicillium	Ash, beech, birch, hickory, oak, poplar, elm Plantain, sorrel Grasses Ragweed Amaranthus, chenopod, cocklebur, Iva, mugwort	Mid-March to Mid-June Mid-May to Mid-June End of May to end of July Mid-Aug. to Frost Early Aug. to Frost	Fire Island, Central Adirondacks (Map furnished by State Health Dept.)
N. Y. (New York) Viestreich	Not important clinically	Timothy Ragweed		None
N. Y. (New York) Westcott	Uncertain	Eastern states group		Central Adirondacks

Ohio (Cleveland) Cohen	*Occasionally* Alternaria	Oak Sycamore Red top, June, orchard, timothy grasses Ragweed	Apr. 20 to May 10 May 1 to June 10 May 15 to June 30 Aug. 1 to Sept. 20	None
Ohio (Cleveland) Rudolph	Contributing causes: Alternaria	Timothy Ragweed	May 15 to July 10 Aug. 1 to Oct. 10	None
Ohio (Cleveland) Weitz	Alternaria Hormodendron	Hardwood trees Timothy, June grasses Plantain Ragweed	March 1 to June 15 May 1 to July 28 May 15 to Sept. 1 Aug. 10 to Oct. 1	None
Ohio (Columbus) Forman	*Occasionally important* Alternaria	Maple, elm Timothy, blue grasses Ragweed	Not as long as stated in texts	None
Ohio (Toledo) Figley	*Very important* 7 to 10 per cent of seasonal cases due to mold alone Alternaria Hormodendron	Trees, chiefly maple June, timothy grasses Ragweed	March to April or May May 20 to July 20 Aug. 15 to Frost	None
Ore. (Portland) Moore	None	Hazel, willow, birch, alder, ash, oak, maple Orchard, rye, velvet, blue, red top, timothy grasses Plantain, mayweed, dandelion, sorrel, lamb's quarters, pigweed No ragweed	Feb. to April March to July May to Sept.	Mount Hood area and Seacoast
Pa. (Philadelphia) Blumstein	*Important* Alternaria Hormodendron Helminthosporium Fusarium	Oak, sycamore Timothy Plantain Ragweed	Late April to late May Early May to early July Early May to early Aug. Mid-Aug. to late Sept.	Atlantic City for molds

TABLE IV—CONT'D

LOCATION NAME	MOLDS	POLLENS	SEASON	POLLEN-FREE AREAS
Pa. (Philadelphia) Bolden	*Exceptionally* Alternaria Hormodendron Aspergillus Penicillium Yeast	Poplar, sycamore, oak Plantain, sorrel Grass Ragweed	March 15 to June 4 Mid-May to Mid-June May 15 to July 15 Aug. 15 to Oct. 1	None
Pa. (Philadelphia) Clarke	*Probably* Alternaria Phoma Macrosporon Aspergillus	Elm, maple, poplar Birch, sycamore, oak, ash, beech, hickory, walnut Grass Sorrel, plantain Ragweed, chenopod, hop Artemesia	March 14 to April 24 April 10 to June 4 May 10 to July 9 May 15 to June 23 Aug. 14 to Sept. 30 Sept. 7 to Sept. 28	Jersey shore for grass and trees
Pa. (Philadelphia) S. S. Leopold	None	Timothy, June grasses, plantain Ragweed	May 15 to early July Aug. 17 to Frost	None
Pa. (Philadelphia) H. C. Leopold	None	Maple, poplar, elm Oak, sycamore Grass Ragweed	March to April Mid-April to May May 1 to Mid-July Aug. 7 to Oct. 1	
Pa. (Philadelphia) Meyer		Same as Clarke		Seashore
Pa. (Philadelphia) Tuft	*Important* Alternaria Hormodendron	Birch, maple, sycamore, oak, hickory Plantain Timothy, sweet vernal grasses Ragweed	March 15 to May 15 May 15 to Aug. 15 May 1 to July 1 Aug. 15 to Oct. 1	None
Pa. (Pittsburgh) Criep	*Important* Alternaria Hormodendron	Timothy, Johnson grasses, plantain Ragweed	May 30 to July 15 Aug. 15 to Frost	None

Pa. (Pottsville) Ricchiviti	*Important in 3 per cent* Alternaria Aspergillus Hormodendron	Timothy, red top grasses Plantain Ragweed	May 28 to July 1 June 10 to Aug. 15 Aug. 15 to Oct. 1	None
Pa. (Ridley Pk.) Baker	In asthma	Oak Grasses Ragweed	April 15 to May 20 May 25 to July 20 Aug. 15 to Sept. 30	None
Texas (Abilene) Sellers	Not convinced	Mountain cedar Mesquite Oak, cottonwood, poplar, elm, pecan Bermuda, Johnson grasses Amaranthus, chenopod, water hemp, Russian thistle Ragweed, common and western	Oct. (worse) to Dec., Jan., or Feb. Late April to July Spring May through Oct. July to Oct. Aug. to Nov.	None
Texas (Dallas) Black	None	Cedar Elm Pecan Bermuda and Johnson grasses Ragweed, Amaranthus, Iva	Jan. and Feb. Feb. and Sept. Early April to July Sept. and Oct.	None
Texas (San Antonio) Kahn	*Clinically in 2 per cent* Alternaria Helminthosporium	Mountain cedar Mesquite Grasses Amaranthus Ragweed	Late Dec. to early Feb. April to Aug. April to Mid-July May to Oct. Sept. to Oct.	Gulf coast in midsummer, Mexico City
Va. (University) Swineford	*Important in some cases* Alternaria	Grass, plantain Ragweed, corn, wheat, rye, oats, goldenrod, cocklebur, alfalfa, chenopod, sheep sorrel	Early May to July Aug. 19 to Oct. 1	None
Wis. (Milwaukee) Light	Alternaria	Timothy Ragweed	June 15 Sept. 8 to 15	None

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND
THEODORE B. BERNSTEIN, M.D., CHICAGO

Studies With Antigens. XIII. The Significance of Reactions to Intracutaneous Tests Performed With Solutions of Purified Extracts of Ragweed Pollens. Efron, B. G., and Boatner, C. H.: J. Invest. Dermat. **5**: 49, 1942.

The purpose of the investigation was to evaluate the significance of reactions to intracutaneous tests performed with solutions of purified ragweed pollens, prepared by a method previously reported by the authors. Forty-five ragweed pollen patients and eighty nonsensitive patients were tested intradermally with 0.02 to 0.0000001 per cent solutions of purified ragweed extract. The incidence of positive reactions in the hay fever group was significantly greater than in the patients of the control series; the conclusion was therefore that these were allergic reactions. Solutions of ragweed extract of 0.02, 0.004, 0.002, and 0.001 per cent used intracutaneously demonstrated clinical sensitivity to these pollens of all but a statistically insignificant proportion of patients. The diagnostic efficiency of the nine dilutions of extracts used did not materially differ and was highest in the 0.001 per cent solution (97.17 per cent ± 1.66 per cent diagnostic efficiency).

The Arm-to-Tongue Circulation Time in Chronic Asthma. Cottrell, J. D., and Cuddie, D. C.: Brit. M. J. **1**: 70, 1942.

The authors call attention to the usual difficulties of differentiating bronchial from cardiac asthma in the presence of cardiac disease. Since it has been previously shown that in cardiac asthma the heart failure is reflected in an increase in circulation time, it is natural to presume that a normal circulation time in an asthmatic patient would exclude the presence of cardiac asthma. In a series of twenty-one patients with chronic asthma without any evident cardiac disease, the circulation time was within normal limits. In four other asthmatic patients in whom hypertension was present as an associated condition the circulation time was also normal. The procedure consisted of an injection of 5 to 6 c.c. of a solution of sodium dehydrochlorate (decholin or suprachol) intravenously through a large needle. The first indication of a bitter taste constitutes the end point. The time between the injection and the bitter taste is called the arm-to-tongue circulation time and varies normally between nine and sixteen seconds. In cardiac asthma it has been reported to vary between eighteen to sixty seconds, with an average of thirty-three seconds.

An Objective Method of Determining Blood Velocity (Fluorescin Method). Fishback, D. B., Guttman, S. A., and Abramson, E. B.: Am. J. M. Sc. **203**: 535, 1942.

It is pointed out by the authors that the majority of methods of determining circulation time are either objectionable because they depend on the uncertainties

of subjective end points or that they are unreliable, expensive, too complex, or even dangerous. They report on the results of a method which depends on the discernment of a brilliant yellow color in the lower palpebral conjunctiva after the intravenous injection of sodium fluorescin. Through an 18-gauge needle, 4 c.c. of 10 per cent or 3 c.c. of 20 per cent sodium fluorescin solution is injected into the antecubital vein. In the darkened room with a portable ultraviolet source and a Wood's filter, the light is directed to one of the eyes. The first appearance of a brilliant yellow color in the palpebral conjunctiva is noted. The time from the injection to this end point is designated as the "circulation time." In individuals without cardiac decompensation, this varied from 7 to 15.6 seconds. In cases of cardiac decompensation, the circulation time ranged from 16 to 25 seconds or even longer. The authors obtained closely approximating results with the magnesium sulfate and the calcium method.

Recent Observations on Hay Fever in Children, Stoesser, A. V.: Lancet **62**: 174, 1942.

The author summarizes his observations and results of treatment of 413 children with seasonal hay fever from 1936 to 1941, at the outpatient department of the University of Minnesota. Of this number 180 began their symptoms before the age of 5 years. The long preseasonal and perennial forms of pollen therapy gave the best results. Coseasonal treatment was unsatisfactory. Those receiving higher maximum doses obtained better results on the average. Out of thirty-six children receiving oral pollen therapy, thirty-three had complete failures. Histaminase orally in twenty-one patients during the season failed completely. Of forty-four children receiving potassium chloride therapy, nineteen had fair results. In none of three cases in which coli metabolin was tried was there any benefit.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MURRAY ALBERT, M.D., BROOKLYN

Sensitization to Horse Serum by Means of Adjuvants. Freund, J., and McDermott, K.: Proc. Soc. Exper. Biol. & Med. **49**: 548, 1942.

Guinea pigs were sensitized by combining horse serum with a lanolin-like substance (aquaphor) and suspending the combination in paraffin oil containing killed tubercle bacilli. They were tested by the intracutaneous injections of different dilutions of horse serum at various time intervals following the sensitizing injection. A control series of guinea pigs was injected with horse serum alone. The adjuvants influenced the sensitization to horse serum in a manner similar to that produced when living tubercle bacilli and horse serum were used. Sensitization was much more easily accomplished when the antigen was combined with aquaphor and then suspended in paraffin oil containing killed tubercle bacilli than when aquaphor was omitted as part of the adjuvant. It was concluded that the use of adjuvants modified the sensitization to horse serum in guinea pigs in several ways: (1) The reaction following the intracutaneous injection of horse serum was usually necrotic and lasted longer than forty-eight hours; (2) The length of time during which the animals remained highly sensitive was usually prolonged; (3) The precipitin titers in the blood were higher in animals sensitized with the use of adjuvants.

Studies on Antibody-Antigen Mixtures. I. Effect on Normal Living Excised Tissue. Kulka, A. M.: J. Immunol. 43: 273, 1942.

An experimental method for studying the effect of antibody-antigen mixtures on normal living excised tissue is described. The uterine horns of normal virgin guinea pigs were suspended in Dale baths, the antibody-antigen mixtures to be tested were added to the baths, and the effects on the uteri were recorded graphically. The antigens employed consisted of egg albumin, codfish, milk, and ragweed proteins, and protein-free polysaccharides. The antisera were obtained from actively or passively sensitized rabbits and guinea pigs. The human antisera were obtained from six patients sensitive to egg, milk, codfish, and ragweed. In the preparation of the antigen-antibody mixtures, the serum was allowed to stand for twenty-four hours before use since fresh serum induced nonspecific contractions of the uteri. Equal amounts of various dilutions of antigen solution and antiserum were incubated for one hour at 37° C. Before the antibody-antigen mixtures were added to the baths, the following steps were taken: First, normal serum of the same species and of the same dilution as that used in the Ab-A mixture was added to the bath to rule out nonspecific reactions. Then the bath was changed and antigen of the same kind and concentration as that used in the Ab-A mixture was added as a control. The next step was the addition of histamine solution to test the viability of the strip. Finally, after changing the bath, the Ab-A mixture was added. Then the bath was again changed and the same specimen was used for testing other mixtures.

Contractions occur in isolated uterine horns of normal guinea pigs when antibody-antigen mixtures are added to the Dale bath. The reaction is apparently due to attachment or absorption of the antibodies by the cells and their subsequent reaction with the antigen. The specificity of a reaction was demonstrated by the fact that the subsequent addition of larger amounts of the same antibody-antigen mixture failed to produce any further contractions. The amounts of antibody and antigen, and the method of administration of antigen (i.e., fractional doses) were factors which influenced the results. When a nonprotein antigen such as type-specific pneumococcal polysaccharide was used, it was found that the Ab-A reaction depended on a quantitative relationship between antigen and antibody, and, in addition, on a serum factor which apparently is complement since the addition of fresh normal serum to antiserum restored its effectiveness in producing contraction.

Experiments on Transfer of Cutaneous Sensitivity to Simple Compounds. Landsteiner, K., and Chase, M. W.: Proc. Soc. Exper. Biol. & Med. 49: 688, 1942.

Guinea pigs were sensitized to picryl chloride by injections of guinea pig stromas treated with picryl chloride in conjunction with intraperitoneal injections of killed tubercle bacilli. About three weeks following the beginning of sensitization, these animals were injected intraperitoneally with killed tubercle bacilli or with tuberculin in order to produce exudates.

These exudates were, in turn, injected intraperitoneally into normal animals. When these animals were tested by the application of a drop of an oily solution of picryl chloride, most of them showed a sensitivity to this chemical. This sensitivity manifested itself by the appearance of an erythematous reaction the next day. It was apparent that the sensitivity was transferred by the sediment of the exudate rather than by the clarified fluid, and that it resided in the cells of the exudate or in antibodies carried by them. When the cells in the exudate were killed by heating, it was impossible to transfer sensitivity. The authors also sensitized guinea pigs by intensive treatment with intracutaneous injections of citraconic anhydride in oil.

The sera of these animals, when injected intraperitoneally into normal guinea pigs, rendered them sensitive. Scratch tests made on these animals with a drop of citraconic anhydride in dioxane were positive. Potent sera of guinea pigs sensitized to the anhydride passively sensitized the skin of normal guinea pigs so that scratch tests, made on the prepared sites twenty-four to forty-eight hours later, showed markedly positive reactions consisting of swelling, discoloration, and pseudopods. The prepared sites also reacted positively when the antigen in oil was injected elsewhere on the normal skin or subcutaneously. Much larger reactions were obtained in the prepared sites when a conjugate, made with citraconic anhydride and guinea pig serum, was injected subcutaneously. The writers are investigating the possibility of the presence of an anaphylactic antibody in the sensitizing sera.

Studies on Chemical Nature and Standardization of Pollen Antigen. Rockwell, G. E.: J. Immunol. **43**: 259, 1942.

The various methods of standardizing pollen extracts and the literature on the nature of the pollen antigen are reviewed. The author emphasizes the fact that none of the methods of standardization are entirely satisfactory because the exact chemical nature of the pollen antigen has not been determined.

A series of experimental studies on the separation and purification of pollen antigen were undertaken. Oxidation with H_2O_2 or the addition of sufficient alkali to ragweed pollen extract destroys its skin-reacting capacity. Strong acids, such as hydrochloric acid, do not destroy the pollen antigen but merely combine with it to form the hydrochloride which precipitates. The writer used this reaction as a means of separating and purifying the pollen antigen. The pollen-antigen-hydrochloride, which was purified and prepared by the author's special technique, was found to be an active antigen in 100 hay fever patients who were skin tested and treated successfully with it. Chemical analysis of the purified, ragweed-pollen-antigen hydrochloride revealed that it had a sulfur content of 7.2 per cent and a nitrogen content of 11.25 per cent. From these figures it could be assumed that the minimal molecular weight of ragweed pollen antigen is 4,453 and that it contains thirty-six nitrogen groups, one SH group, and combines with ten molecules of hydrochloric acid. The pollen antigen is basic in character, even though crude pollen extracts are acid. The basic groups are evidently loosely combined in the native state with some other substance which, when the pollen antigen is precipitated, is left in the extract as a hapten. X-rays of pollen-antigen-hydrochloride suggest that the molecule is complex. The purified antigen is levorotatory. A study of the nitrogen distribution showed that 0.0022 μg of pollen-antigen-hydrochloride nitrogen is equivalent to one Noon unit and 0.0033 μg is equivalent to one protein-nitrogen unit. The author concluded that from its characteristics, the pollen antigen is a polypeptide. It differs, however, from the common polypeptides in that it contains a large percentage of basic amino acids such as arginine and histidine.

The Permeability of the Gastrointestinal Mucosa of Guinea Pigs to Crystalline Egg Albumin. Hartley, G., Jr.: J. Immunol. **43**: 296, 1942.

The problem of the passage of native proteins through the gastrointestinal mucosa of guinea pigs was studied by the collodion particle agglutination method.

Groups of scorbutic and nonscorbutic guinea pigs were fed a single dose of crystalline egg albumin solution. A control group received egg albumin solution by intra-abdominal injection. The animals were bled before and after the administration of the antigen at weekly intervals until the antibody titer of the blood reached

its maximum. The results indicated that the guinea pigs receiving crystalline egg albumin by mouth developed antibody titers as high as those receiving the antigen parenterally.

Two series of guinea pigs, one scorbutic and one nonscorbutic, were sensitized orally by one feeding of crystalline egg albumin solution. The animals were bled three weeks after the initial feeding for antibody titration. Twenty-four hours later, the animals were again fed egg albumin solution and were observed for symptoms of anaphylactic shock. Seventy per cent of the scorbutic and 40 per cent of the nonscorbutic sensitized guinea pigs were shocked by the oral administration of the specific antigen. A definite relationship was found between the circulating antibody titer and the severity of the anaphylactic shock following the oral administration of antigen.

The effect of continued feedings of crystalline egg albumin on the persistence of circulating antibody titers in guinea pigs was also studied. Guinea pigs were fed crystalline egg albumin once a week for several months, and the serum was titrated for antibodies on the day preceding each feeding. It was found that the titer reached a maximum in from three to five weeks after the first feeding, remained at this level one or 2 months and then decreased slowly and disappeared in one or two months, despite the weekly feedings. In an effort to determine whether the antibody-forming mechanism was exhausted by the weekly feedings of antigen, a number of the animals so treated were given an intra-abdominal injection of the antigen from four to five months after the initial oral dose, when the circulating antibodies had disappeared. Within one week after the parenteral injection, all the animals developed precipitins in the blood which passively sensitized normal guinea pigs. This demonstrated that the antibody-forming mechanism was not exhausted by weekly feedings of antigen. The possibility that antigen might be fixed in the sensitized wall of the intestines, thus preventing the passage of antigen into the circulation, was suggested.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

The Classification of Eczematoid Eruptions in Children With Especial Reference to Contact Dermatitis. Hill, L. W.: J. Pediat. **20**: 537, 1942.

One hundred and fifty-six cases of eczema in children from 1 to 17 years old seen in private practice are classified. The nomenclature and classification suggested by Sulzberger, with slight modifications, are used. The group included 105 instances of atopic dermatitis, three of contact dermatitis, three of nummular eczema, and two of circumscribed neurodermatitis.

In the *atopic dermatitis* group, 70 per cent were from 1 to 4 years of age. Vesiculation was apt to be present in infancy and absent later on. Skin tests are difficult at this age, and usually one has to be satisfied with incomplete testing. The author usually does about forty scratch tests followed by a few selected intradermal tests. Indirect testing is seldom done. If the scratch tests are positive, it verifies the fact that the individual belongs in the atopic group and strongly implies that the dermatitis is atopic. The allergens involved may work by ingestion, inhalation, and as Osbourne and Walker have suggested, by direct contact. Hill feels that the

latter seldom occurs unless the epithelium has previously been injured by rubbing or scratching.

The eruption of *contact dermatitis* usually starts on the extremities and may be due to innumerable organic or inorganic substances. It seldom occurs in the infant and is common in the runabout child who characteristically has large skin areas exposed. A sharp line of demarcation at the clothing line is characteristic. Diet therapy is usually tried sooner or later and always fails. Soap is not a common offender, naphthalene (moth balls) and outer winter clothing are more likely causes. Patch tests in general are seldom helpful and can be negative even when the substance responsible for the contact dermatitis is employed due to failure to duplicate all the factors concerned.

In the thirty-one cases of contact dermatitis, the cause of the dermatitis was determined in fifteen. Five were dyes, three were plants, three were toilet articles, and the others were a toilet seat, sulfur, ammoniated mercury, and furniture polish.

Five individuals had both contact dermatitis *and* atopic dermatitis.

Nummular eczema is usually wrongly diagnosed as atopic dermatitis. The etiology is unknown but has nothing to do with allergy. Itching is slight, never severe, and the lesions are sharply defined circular patches, dark in color, the larger ones of which are thick and boggy, though not actually weeping. The patches occasionally are clear in the center and often occur on the extension surfaces of the extremities.

Circumscribed neurodermatitis occurs in older children or adults and consists of one or two lichenified patches of varying size, the margins of which are poorly defined. The primary cause is thought to be itching, followed by such continuous rubbing and scratching that the lesion continues independent of the primary cause.

Recent Observations on Hay Fever in Children. Stoesser, A. V.: Lancet **62**: 174, 1942.

Experience in the treatment of hay fever for the past ten years at the pediatrics outpatient department of the University of Minnesota Hospital is reviewed. The hay fever patients comprised 20 per cent of the allergic group and four-fifths of them were male. Skin tests were done to sixteen groups of pollen by the pressure-puncture method, using sodium hydroxide and dried pollen. There was little relationship between the size of reaction and clinical sensitivity. At the start of treatment each patient was classified as to sensitivity by serial intradermal tests to determine the dosage schedule to be used. While perennial treatment was deemed better, the majority of patients received preseasonal treatment. Ragweed sensitivity occurred more than four times as often as grass sensitivity. The best response to treatment occurred in the tree-sensitive group in which box elder, cotton wood, and oak were the most important pollens. The poorest response occurred in desensitization to grass pollen.

Oral pollen therapy in thirty-six children was almost a complete failure as was histaminase therapy in a group of twenty-one children. On the other hand, potassium chloride in daily doses of 15 gr., together with salt restriction, proved fairly satisfactory. Forty-three children received potassium chloride. Eight were nauseated and discontinued its use, nineteen obtained satisfactory benefit, while sixteen did not. Three children received a *B. coli* filtrate called coli metabolin without benefit.

Allergic Respiratory Disease and Pneumonia in Childhood. Cohen, S.: New Orleans M. & S. J. **94**: 440, 1942.

The most common pneumopathy complicating an attack of asthma in childhood is atelectasis caused by allergic edema and inspissated mucous plugs. It is usually

mistaken for pneumonia. Distal to the plugs, secondary infection with organism normally present occurs, causing fever and other constitutional manifestations of infection. The prognosis, however, is good and response is often surprisingly rapid if the patient is separated from the allergens to which he is sensitive. Further help comes from rehydration and drugs, especially ipecac in emetic doses. Emesis induced by ipecac often liberates mucous casts and allows aeration of the blocked area of the lung to occur. Sulfonamides, on the other hand, are likely to be of little or no help.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Vernal Conjunctivitis. A Brief Review of the Literature. Eber, Carl T.: J. Missouri M. A. **39**: 171, 1942.

In a brief review of the literature on vernal conjunctivitis, Eber calls attention to some of the most outstanding observations on this subject. He concludes, however, that vernal conjunctivitis is still a disease of unknown etiology in spite of the fact that there is definite evidence that it has the characteristics of an atopic disease.

It has been our experience that true vernal conjunctivitis is rarely associated with other manifestations of allergy. Conversely, conjunctivitis associated with other manifestations of allergy, particularly the nasal type, does not conform to the classical vernal conjunctivitis.

Histamine in the Treatment of Nasal Allergy (Perennial and Seasonal Allergic Rhinitis). Farmer, L., and Kaufman, R. E.: Laryngoscope **52**: 255, 1942.

Farmer and Kaufman present further observations on the use of histamine in the treatment of nasal allergy. Both seasonal and nonseasonal types were treated. The histamine was given by subcutaneous injection, the initial dose being about 0.01 to 0.1 gamma. The highest dose in perennial rhinitis was 100 gamma. The effectiveness of small doses was emphasized. Injections were increased each time by 50 per cent if well tolerated. In the beginning they were given two to three times a week. Later they were spaced at approximately 5-, 7-, 10-, 14-, and 21-day intervals. It was also emphasized that doses must be individualized. Among forty-one cases of perennial rhinitis, in twenty-five the result was good, in ten fair, and in six poor. Among fifteen of the forty-one severe cases, however, ten had a good result. In the treatment of uncomplicated cases of tree, grass, and ragweed hay fever, injections were started ten weeks before the onset of the season. During the first month the injections were given twice a week, thereafter once a week, and continued at this interval until the end of the season. The initial dose in this group was 1 gamma. If the injections were well tolerated, subsequent doses were 2, 4, 8, 15, 30, 50 and 75 gamma. These eight doses were given during the first month of treatment at about four-day intervals. The ninth to the fourteenth doses were 100 gamma each and were given at an interval of one week. At the beginning of the pollinating season the dose was reduced to 30 gamma and, if well tolerated, continued with this amount at weekly intervals to the end of the pollinating season. Among seventy-two ragweed cases, of which twenty-four were considered severe, seven had good results and nine fair results. Among forty-eight cases of ragweed

considered as moderate, nineteen had good results and thirteen fair. Among fifteen cases of grass hay fever, four were severe and eleven moderate. Nine had a good result and six fair. The same satisfactory results were obtained in tree pollinosis.

Physical and Chemical Properties of Sputum; (2) Influence of Drugs, Steam, Carbon Dioxide and Oxygen. Basch, F. P., Holinger, P. H., and Poncher, H. G.: Am. J. Dis. Child. **62**: 1149, 1941.

The Influence of Expectorants and Gases on Sputum and the Mucous Membranes of the Tracheobronchial Tree. Basch, F. P., Holinger, P. H., and Poncher, H. G.: J. A. M. A. **117**: 675, 1941.

The physical and chemical properties of sputum and the factors determining variations in portions from different parts of the tracheobronchial tree were studied by Basch, Holinger, and Poncher. It was noted that sputum from the most dependent parts of the bronchi had an extremely high viscosity and could be obtained only by bronchoscopic aspiration. The secretion at a higher level was considered the secretion from below, liquefied and with a lower solid content. On top of this secretion after a rest period there was found a plug with moderately high viscosity. The various factors which influenced the character of the secretions were selective secretion, selective resorption, the speed of movement of secretion from one level to another, and bacterial action. The investigators also studied the influence of the commonly used expectorant drugs, oxygen, steam, and carbon dioxide in the sputum in different areas of the trachea and bronchi and on the mucous membranes. Ammonium chloride, potassium iodide, fluid extracts of senega and ipecac and emetine hydrochloride liquefied the sputum in the upper bronchi but did not influence the material in the peripheral bronchi. Steam inhalations in an atmosphere at 70 to 75° F. of 80 to 90 per cent relative humidity liquefied the secretions throughout. Carbon dioxide inhalations liquefied secretions and stimulated resorption. Thus carbon dioxide and steam may be considered as extremely efficient expectorants. Oxygen, on the other hand, unless humidified or diluted with 10 per cent carbon dioxide, thickened the secretion, as did atropine sulfate and codeine, and consequently oxygen must be considered as an antiexpectorant when administered in the treatment of respiratory obstruction complicated by pulmonary suppuration.

Allergy as a Contributing Factor to Biologic Deafness. Mao, Chun-yue: Arch. Otolaryng. **35**: 582, 1942.

In studying the incidence of allergy in biologic deafness and pathologic deafness, Mao concludes that in the pathologically deafened children, with their equally high incidence of allergic manifestations, it may be assumed that the hereditary factor of allergy renders them constitutionally more susceptible to the influence of various contagious and infectious diseases. He believes that definite evidence has been offered to indicate a higher percentage of allergic reactions in deafened children than in children with normal hearing. Allergy has been shown to be a hereditary disease in a high percentage of children so afflicted. He finally concludes that it is not unreasonable to assume that allergy and deafness have some mutual hereditary background.

Specific Vaccine Therapy in Treatment of Sinusitis. Cohen, Myer Solis: Arch. Otolaryng. **35**: 623, 1942.

Cohen presents his observations and experiences in the preparation and use of vaccines in the treatment of sinusitis. He states that when sinusitis develops

in allergic persons, the secondary effects frequently take the form of bacterial allergy, with asthma and allergic rhinitis as the prominent manifestations. He further states that vaccine therapy may be of no benefit in persons with chronic sinusitis when there is suppuration in a sinus that is not draining or that drains poorly or when the sinusitis is secondary to an untreated primary focus of infection, such as diseased tonsils. The observations in this paper were confined entirely to vaccine therapy. Nothing was said about the management of the allergic cases from the standpoint of pollen, food, or inhalant allergy.